ANNUAL REVIEW OF MEDICINE

ANNUAL REVIEW OF MEDICINE

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PREFACE

In expressing our gratitude to those who have so generously collaborated in the authorship of this present volume, we wish to thank again those who wrote for the first volume of the *Review*. The ability of these first two groups to present the advances in their respective fields will be an example to future authors. They have set the necessary precedent of writing instead of cataloguing, and of surveying the field and at the same time stressing that portion of it in which their special talent and interest lay.

It is greatly to be regretted that we have been unable to include three manuscripts, that on Endocrinology by John S. L. Browne for Volume I and those on Endocrinology and on Pediatrics by Allan T Kenyon and Allan M. Butler, respectively, for Volume II. Unforeseen difficulties have made it impossible for these to be prepared in time for publication.

The editors are most appreciative of the assistance and support of the Annual Reviews office staff, including Carol F. Kupke, Robbie Bass, Barbara C. Darneal, and Joyce V. Fairweather.

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ANNUAL REVIEW OF MEDICINE

VOLUME III (1952)

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INFECTIOUS DISEASES[1]

Viral and Rickettsial Diseases

By F. M. Burnet

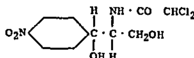
Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

In preparing this review, it has been considered advisable to restrict consideration to a relatively small number of conditions in regard to which important advances have been made in the period under review. As a convenience both to the reader and the reviewer, the procedure has been adopted of discussing only publications which have appeared subsequent to those referred to in *Viral and Rickettsial Infections of Man* (134). The main sections of the review are concerned with topics in which advances significant for public health or clinical medicine can be reported. At the same time it has been thought advisable to include a brief final section dealing with recent laboratory work on viruses which seems likely to influence significantly the future development of virology.

The Use of Chloramphenicol and Aureomycin in the Therapy of Rickettsial and Viral Disease

Preliminary accounts of chloramphenicol (Chloromycetin) appeared in 1947 (1) suggesting that it would be found effective in rickettsial as well as bacterial disease. Subsequent experience has fully substantiated its value in rickettsial infection of several types. Aureomycin has been introduced during the last two years and has also shown itself effective in a broadly similar field

Chloramphenicol.—This antibiotic, originally obtained from the mould *Streptomyces venezuelae*, has now been shown (2) to have the constitution



and has been synthesized (3). The synthetic material, in addition to having the same physical properties, is indistinguishable from that produced biologically in tests on experimental infection and in its clinical activity on scrub typhus (4).

Experimental studies of chick embryos infected with various rickettsiae showed that all were inhibited to some extent in the sense that the survival time of the embryo was increased The order in which the experimental rickettsial infections were influenced starting from the most sensitive, was scrub typhus, rickettsial pox, murine and epidemic typhus, rocky mountain

[1] This review covers approximately the period from January, 1948 to June, 1950.

spotted fever, and Q fever, the last being the least influenced (5) Scrub typhus (*Rickettsia tsutsugamushi*) has been the disease most actively studied both experimentally and clinically in regard to the action of chloramphenicol, and it will be discussed here more fully than the others.

Tests of chloramphenicol in mice showed undoubted effects, particularly when the strain "Karp" was used; but treatment had to be prolonged, and although the mice survived after being given many lethal doses, the rickettsiae persisted in the spleen for at least 100 days. The other standard strain "Serangayee" was much more resistant to therapy. The drug had no effect at all *in vitro* (5).

The *results of prophylactic treatment in human volunteers are instructive* and may be dealt with first. The volunteers used by Smadel *et al.* (6) remained in a region heavily infested with infected mites for several days during which the experimental group took 1.0 gm. chloramphenicol daily, this dosage being continued for 20 days in all. The unprotected control subjects showed infection of 71 per cent within this period. None of the experimental subjects showed symptoms until about 10 days after cessation of the drug when 55 per cent became infected.

The clinical use of chloramphenicol in Malaya (7, 8) has been uniformly effective, recovery following within one or two days, even in desperately ill patients. Most cases on admission had been ill for several days (average 6). They were given an initial dose of 3.5 gm. by mouth followed by 0.25 gm. at two-hour intervals for 24 hr. Defervescence with great clinical improvement followed rapidly, the average time required being 32 hr. as against about 14 days of illness in the average untreated case. In the last available statement (8), no deaths have occurred in 100 treated cases, the normal Malayan death rate from scrub typhus being 7 per cent. A recent paper from Malaya (9) describes equally satisfactory results from a single dose of 3 gm. of chloramphenicol by mouth.

Good results, not quite so dramatic as with scrub typhus, have been described for epidemic typhus treated with chloramphenicol in Mexico (10) and Bolivia (11) Rocky Mountain spotted fever (Eastern type) also responds dramatically. All of 15 patients, 4 of whom were severely ill, became afebrile within 76 hr of the commencement of therapy irrespective of the stage of the disease. This contrasts with a mortality of 21 per cent and an average duration *of illness in uncomplicated cases of 16 days during the* preceding years in Maryland.

Laboratory experiments (5, 12) showed a *significant increase in the survival* of chick embryos inoculated into the yolk sac with psittacosis or lymphogranuloma venereum viruses and treated with chloramphenicol. In mice, the situation closely resembled that obtained with scrub typhus *infections*. Good protection in the sense of survival was afforded against intraperitoneal infection with psittacosis virus, none against intracerebral infection. There was no virucidal effect *in vitro*, and with neither organism was infection eliminated from the mice.

Aureomycin.—The discovery of aureomycin was announced in 1948, and an extensive collection of reports on the properties and therapeutic activity of the drug was presented at a symposium of the New York Academy of Sciences (13). It is a crystalline yellow compound prepared from cultures of a new Streptomyces (*S. aureofaciens*) and having probably the widest spectrum of action of any of the antibiotics yet produced commercially.

The action of aureomycin on rickettsial and viral infections is essentially similar to that of chloramphenicol. In laboratories, experimental infections by the rickettsiae and the organisms of the psittacosis group are controlled (13). According to Wells & Finland (14), the action of aureomycin on psittacosis infection in chick embryos is significantly better than that of chloramphenicol.

Clinical studies on the therapy of rickettsial disease have been reported for epidemic typhus in Mexico (15). "Remarkable improvement in all signs and symptoms" was evident in the first 24 hr. with all patients, and the rash faded in two to three days. Equally impressive results were obtained in Rocky Mountain spotted fever (Eastern type) using a dosage of 60 mg. per kg. daily in divided doses (16) Schoenbach (17) found a single case of recrudescent, epidemic typhus (Brill's disease) to respond satisfactorily. Lennette and collaborators (13) obtained a good therapeutic effect in Q fever, but the mildness and variability of this disease makes it difficult to assess the significance of the result

There is evidence of effective therapy in the treatment of lymphogranuloma venereum (18, 19), the most interesting feature being the control of acute proctitis and diminution of the symptoms associated with rectal stricture in women

There is now a large body of evidence to show that aureomycin is an effective therapeutic agent in primary atypical pneumonia. Meiklejohn & Shragg (20) treated 38 patients, half with penicillin alone, half with aureomycin. Most of the latter showed a rapid defervescence, 13 of 18 treated with aureomycin becoming afebrile within 48 hr of the commencement of treatment as against 6 of 20 in the penicillin series. Three of the aureomycin cases showed a temporary relapse on discontinuance of the drug. Four patients who were very ill on penicillin alone responded satisfactorily to aureomycin when this was administered

Finland *et al.* (21, 22) had an equally gratifying experience in Boston although in this study, no control group was used. Almost all the treated patients became afebrile or showed a major drop of temperature within 48 hr., 31 out of 40 showing symptomatic improvement in less than 24 hr. The dosage used in this series was 1.0 gm every 4 to 6 hr until the temperature was normal, and then every 6 to 8 hr for two to three days, the total amounting in most cases to 10 to 15 gm The cases tested were of more than average severity, and 32 of 40 showed significant titers of cold agglutinins

Another series of cases studied by Schoenbach & Bryer (23) showed

prompt improvement with a lower dosage of 2 gm. per day for 4 days. Brief reports (24, 25) indicate that chloramphenicol is also effective in the treatment of primary atypical pneumonia Although there is no indication that aureomycin has any influence on influenza virus, Finland *et al.* (26) report that in the influenza A prevalent in Boston in March, 1949, there were a considerable number of relatively sick patients on the third to fifth day of illness who responded rapidly to aureomycin

Finland *et al.* (27) also describe an active therapeutic effect of aureomycin in herpes zoster given in doses of 4 gm. per day. The best results were seen in patients healed before the middle of the second week. In general, there was great relief of pain even in ophthalmic herpes, and a considerable number of cases showed an onset within 24 hr. of rapid evolution and clearing of the eruption. There were, however, a number of cases who responded poorly, and it has been reported [Schoenbach (28)] that zoster may appear in the course of aureomycin therapy. It seems, therefore, that further series of fully controlled tests should be carried out on this condition.

Claims that aureomycin is of value in infectious mononucleosis (29) have not been substantiated in a small controlled study by Seiffert *et al* (30).

Poliomyelitis

In view of the rapidly increasing number of isolations of neurotropic viruses from a variety of sources and the confusion which has arisen over the use of terms such as mouse poliomyelitis virus, an authoritative committee on nomenclature (31) has offered the following provisional definition.

> The term Poliomyelitis virus should be used to designate strains of the agent originally described as the cause of poliomyelitis in man and only these It may be identified by the characteristic experimental disease produced in the monkey, by the character and distribution of histological lesions in the spinal cord and brain of infected primates and by its host range and immunological properties

Within the limits of this definition, it has now been accepted that there are three immunologically distinct types of virus. The majority of strains recently isolated in the United States fall in Group I of Kessel & Pait (32), the strain "Brunhilde" being taken as the type of the group. Group II, including "Lansing" and "MV," is rarer and contains all the strains that have been adapted to rodent passage Group III at present is limited to one strain, "Leon," isolated in Los Angeles in 1937.

The immunological differentiation of these types can be demonstrated by reinfection experiments in recovered monkeys (32, 33), by challenge of vaccinated animals (32, 34), by neutralization of virus with immune serum (32), and by a serum flocculation test using virus partially purified and precipitated with protamine (35) This work underlines the fact previously realized that serological surveys using the mouse-adapted Lansing virus provide no direct information about the spread through the community of the important viruses of Group I (36, 37).

Two types of laboratory investigations which may shortly have practical repercussions are represented by the studies in Enders' laboratory (38) on the growth of poliomyelitis viruses in human tissue cultures and by the finding that one of the mouse encephalitis viruses, GD VII, will agglutinate human erythrocytes (39). It has also been claimed that "Lansing" strain will agglutinate sheep red cells (40).

Epidemiology.—An outbreak of poliomyelitis in an Eskimo community in Arctic Canada (41) has again shown the characteristic behavior of the disease in a "virgin soil" community. In the Chesterfield region on the West side of Hudson's Bay, 14 per cent of the population was paralyzed and 5 per cent killed by the epidemic. Symptoms of infection not reaching the paralytic level were very common: "In some camps and in some families everyone except the babies had symptoms." No child under three years showed paralysis, and the incidence in the group under five was only one-tenth of that in the age group 15 to 19 which showed the highest incidence, 42 per cent The picture is almost identical, except for the higher virulence of the infecting virus, with that observed in the outbreak at St Helena in 1947 and should be contrasted with the Malta epidemic of 1942 to 1943 where almost all the reported cases were in children under five. A somewhat similar epidemic has been described from the Nicobar Islands (42) in a tropical region as far removed as possible from the sub-zero weather prevailing during the Canadian epidemic.

There is a growing feeling that the epidemiology of poliomyelitis is largely determined by the intensity of subclinical infection with the virus in infancy. Few writers would, however, go as far as the reviewer (43) in ascribing the changes in the distribution and age incidence of poliomyelitis that have been seen in the last 40 years to the steadily improving fecal hygiene of infancy with its gradual reduction of immunizing infections at the age least likely, to judge from virgin soil epidemics, to produce paralytic infections Dauer (44) finds a steady diminution in the proportion of deaths from poliomyelitis in the United States, falling in the under-five group over the period 1920 to 1944 In Britain, there was no evidence that the incidence of poliomyelitis in 1947 was correlated either positively or negatively with the general infantile death rate (45).

On the other hand, Hammon *et al* (46) have compared the incidence of Lansing type antibody in children of different social levels in California and from the Pacific island, Guam Taking the group of children from seven to nine years, he obtains figures for well-to-do Californian families of 21.7 per cent and 38 6 per cent in San Francisco and Bakersfield, respectively, of 52 per cent and 74 per cent for poor Californian families, and of 95 per cent for Guam. No surveys for antibody against Type I (Brunhilde) virus have been reported, but Bodian (47) has shown that gamma globulin from pooled human serum is approximately equally and highly active in neutralizing all three serological groups of viruses It is not unlikely, therefore, that immunization of the community by each type is proceeding at similar rates

Important indications of the part played by intestinal infection in relation to subsequent immunity may be drawn from experiments on chimpanzees reported by Howe, Bodian & Morgan (48) and by Melnick & Horstmann (49). When virus has been fed to previously untreated animals, it remains demonstrable in the feces for up to eight weeks and may also be isolated from pharyngeal swabs. In most such animals, despite the absence of symptoms, lesions can be found in the central nervous system after careful histological study, and all showed a development of serum antibody. When a second attempt to infect animals with the same serological type was made, the carrier state could only rarely be induced. If first infection was with Group II virus (Lansing), a second feeding with the heterologous Group I virus (Brunhilde) gave the same proportion of carriers, with a few paralytic cases, as would be expected if it had been administered to normal chimpanzees.

Nothing that has been recently published appears to be incompatible with the view that the situation in the chimpanzee presents the best model of what occurs in children. On that basis, it might be suggested again (*a*) that first infection during infancy is less likely to result in paralysis than at any other age, (*b*) that an epidemic of poliomyelitis showing a concentration of cases in the infantile group is one occurring in a community which has been heavily infected throughout the immediately preceding years, usually at a subclinical level, so that all older children are immune, and (*c*) that a rising age incidence and an increased absolute level of symptomatic poliomyelitis in a civilized community are indicative of improving fecal hygiene in infancy with postponement of immunizing (and/or paralytic) infection.

Factors predisposing to paralysis.—There is now substantial evidence (50, 51) that excessive exercise during the period of onset of symptoms is liable to accentuate the degree of paralysis in the limbs concerned. This may be related to the important finding that in both Australia and England, immunization, especially with combined pertussis-diphtheria antigens, may result in sharp localization of paralytic poliomyelitis to the inoculated limb

Reports of paralysis following immunization have been received from time to time, and Martin (52) has analyzed all the available reports from English centers since 1941. In general, there is unilateral paralysis of muscles of the injected limb coming on within four weeks of inoculation. In the 80 cases analyzed by Martin, there was no final evidence as to the nature of the paralysis, but the accompanying constitutional symptoms and the changes in the cerebrospinal fluid suggested that many of them represented poliomyelitis The seasonal and geographic incidence of these cases showed a close coincidence with the incidence of poliomyelitis in the country.

In Australia, McCloskey (53) observed in the course of the 1949 epidemic in Victoria a number of instances in which children showing severe paralysis in one limb gave a history of having received a prophylactic immunization of some sort in that limb one to two weeks previously. A careful study of all

cases of poliomyelitis which had been given any type of injection in the preceding three months fully confirmed this impression. Of 21 children given pertussis or combined pertussis-diphtheria antigens over that period, 20 showed moderate to complete paralysis in the limb last inoculated The time between the last inoculation and the onset of poliomyelitis was distributed as follows: 4 days, 1 case; 7 to 16 days, 13 cases; 20 to 32 days, 6 cases There was significant but less striking evidence that immunization with diphtheria antigens (alum precipitated toxoid) might also be associated with the onset of paralysis 7 to 20 days later.

At a meeting in London, the full figures for Victoria in 1949 were provided by Burnet (54) from unpublished data by McCloskey. These figures indicate that in an epidemic of 792 cases, 31 were associated with pertussis or combined pertussis-diphtheria immunization in such a way as to indicate that the injection had a direct relation to the paralysis, and probably 10 were similarly related to diphtheria immunization. Geffen (55) described essentially similar experiences in the St. Pancras district of London, and Hill (56) gave the preliminary results of a survey of the incidence of poliomyelitis in relation to immunization in a number of English sanitary districts. These results indicated unequivocally that recent inoculation in the presence of a poliomyelitis epidemic increased the likelihood of paralytic infection and largely determined the site of paralysis. At this meeting the reviewer discussed the possible pathogenesis of the condition. The possibility of the virus being introduced with the injection can be excluded, and it is out of line with current views on poliomyelitis to believe that virus circulating in the blood should localize and multiply in inflammatory tissue around the inoculum. Everything points to the likelihood that in some way, the traumatic, toxic, or inflammatory local lesion produced by the inoculum induces a state of vulnerability in the anterior horn cells of the corresponding region of the spinal cord. It is by no means easy to see the mechanism by which the motor cells can be influenced, and much experimental work in this field is called for.

There is, however, an increasing body of evidence that the concept of functional differences in vulnerability of nerve cells is legitimate and valuable in the interpretation of the phenomena of human poliomyelitis. The finding of Howe & Bodian (57) that following section of one sciatic nerve in monkeys, anterior horn cells corresponding to the motor fibers of the cut nerve do not show histological evidence of damage by poliomyelitis virus, remains the most important experimental basis for the view The evidence previously referred to (50, 51) that excessive exercise favored the localization of paralysis points in the same direction In general, a quiescent cell seems to be resistant to damage by the virus, one under stimulus or exhaustion more susceptible.

No information has been published as to American experience in regard to any relationship between immunization and paralytic poliomyelitis. Only when such an analysis is available will it be possible to attempt an

answer to the many problems raised by the Australian and English occurrences.

THE COXSACKIE VIRUSES

The discovery by Dalldorf and collaborators (58) of a new type of virus responsible for human disease is the most important single event in the field of virus diseases to be recorded for the period under review. The first human case from which the virus was isolated was found in the small town of Coxsackie in New York State, and Dalldorf (59) has given the name Coxsackie virus to a group of agents present in certain samples of human feces primarily characterized by their capacity to infect the muscular tissues of newborn mice

The virus was first found in the course of attempts in 1947 to isolate mouse-pathogenic strains of poliomyelitis virus from the feces of patients with nonparalytic infections. In two instances, a virus pathogenic for suckling mice was obtained which produced lesions both in the muscles and in the central nervous system. Virus was present in large amount in the infected muscles and in smaller amount in the brain. Convalescent serum from the two patients providing the virus was capable of inactivating the virus, thus giving *prima facie* evidence that the virus had been responsible for the disease, diagnosed clinically as nonparalytic poliomyelitis, from which they had suffered Numerous isolations of the virus have since been reported (58, 60, 61). It appears to have been widespread in northeastern United States during 1947, 1948, and 1949, and serological evidence of its presence in England in the autumn of 1949 has been obtained (62).

The laboratory characteristics of the virus are as follows: It is pathogenic for newborn mice, but produces no lesions in mice more than 12 days old, baby hamsters are similarly infected The capacity to produce infection of voluntary muscle cells appears to be limited to viruses of this group, but the possibility, in fact probability, that viruses of the same general character will be found in the feces of mice or other animals will need to be kept in mind The virus is one of the smallest known, being probably about 10 mμ in diameter [Quigley (63)]. Serological tests may be made either by a neutralization technique (58) in which virus-serum mixtures are inoculated into suckling mice or by complement fixation, preferably with purified antigen made from infected muscle tissue (61, 62, 64). Both tests indicate the existence of distinct serological types which have been designated 1, 2, 3 (65), 4, 5 (61). From the limited information yet available, type 1 has been isolated in New York state in 1947 and Georgia in 1949, type 2 has been present in 1947 in Wilmington, Delaware, in New York state in 1948, and in Georgia and Great Britain in 1949; type 3 has been found only once in New York state; types 4 and 5 were isolated in Georgia in 1949.

Cynomolgus monkeys can be infected with at least one type of Coxsackie virus by oral administration (66). They develop a virus-carrier state, show

some fever, and develop antibody; the virus is present in their feces, but not in swabs from the nasopharynx. In chimpanzees, it can be similarly implanted in the intestine with the appearance of circulating antibodies; in this species, the virus can be reisolated from the throat (60) Rhesus and cercopithecus monkeys are insusceptible, either orally or intracerebrally (66).

Coxsackie viruses have been isolated from persons showing two different clinical syndromes, one identical with what is normally diagnosed as nonparalytic poliomyelitis, the other that which has been described as Bornholm disease, epidemic pleurodynia or epidemic myalgia. Melnick *et al.* (60) studied 19 cases of "nonparalytic poliomyelitis" and found 12 to give evidence either by isolation of the virus or by serological test that Coxsackie virus was concerned. Poliomyelitis virus was not isolated from any of these 12 cases but from two of the other seven cases. There is a good deal to suggest that a relatively large proportion of what was diagnosed poliomyelitis in North America in 1947 may have been the result of a concomitant epidemic spread of the new virus.

In Milwaukee, Fox & Wallace (67) described 87 cases of nonparalytic poliomyelitis which might well have been of Coxsackie type though no experimental studies were made. A Toronto group (68) found that an unduly small number of poliomyelitis virus isolations could be made from the nonparalytic cases of the current epidemic. There was a suggestion that minimal lesions were being produced in the central nervous systems of monkeys injected with "negative" stools.

In Cincinnati, Sabin & Steigman (69) described a widespread epidemic of "summer grippe" characterized by fever, headache, nausea, vomiting, and sore throat, with complete recovery within three to seven days. Stools from 10 of these cases gave one typical poliomyelitis virus and four strains of extremely low virulence. In a study of the same material preserved, Melnick *et al* (70) obtained three Coxsackie viruses. Antibody tests appeared to speak against the likelihood that the summer grippe was a manifestation of Coxsackie virus infection. This type of finding emphasizes the widespread presence of both poliomyelitis and Coxsackie viruses in feces during the summer season, and the reservations which must be maintained as to the significance of virus isolation in any given case.

Epidemics of Bornholm disease have been frequently described in recent years and have presented an etiological problem of great interest because of the indication that the lesion was located in voluntary muscle. It is, perhaps, premature to say that the Coxsackie viruses are responsible for the disease, but the evidence is pointing strongly in that direction. Curnen *et al* (71) and Findlay (62) have described accidental laboratory infections with the virus which gave typical symptoms. Cases from a number of small epidemics in Britain during autumn, 1949, have shown positive complement fixation tests to Dalldorf's type 2 virus (62) It is reasonably certain that by the time this review appears in print the position will have been clarified.

Respiratory Infections

Influenza.—Influenza outbreaks have been reported in the last three years from various parts of the world. The most noteworthy was the extensive epidemic of Influenza A in Europe during January, 1949. This has been described briefly in a lecture by Andrewes (72) but has not been comprehensively described elsewhere. It was apparently first reported in Sardinia, then in Sicily and southern Italy. The epidemic spread up Italy into Switzerland, Austria, and France and a little later involved Germany, Belgium, Holland, and northern Spain. In most of these countries, there was a high incidence of infection. In England, there was some influenza, but it appeared later than on the Continent and was not extensive An army outbreak was described by Milne & Cruickshank (73) from which Influenza A virus was isolated. In America, little influenza was reported, but Finland *et al.* (74) state that there was a prevalence of Influenza A in Boston in March, 1949.

An isolated but severe Influenza A epidemic has been described from Ocean Island in the Central Pacific (75) This epidemic had a number of interesting features, especially the fact that it followed the arrival of a ship carrying Chinese laborers who had no evidence of influenza during the voyage and were not affected by the epidemic when it broke out among the Gilbert and Ellice Islanders who made up the rest of the labor force on the island. Among the latter groups, the incidence was very high, and there were a few deaths Influenza A virus of A prime type was readily isolated and corresponding serological evidence obtained.

Another Influenza A epidemic of similar character among Eskimos of the far north of Canada has been described by Nagler *et al* (76). All individuals in the group were involved, and there were 18 deaths (20 per cent) though this high mortality was probably due to the lack of medical care rather than to any excessive virulence of the virus concerned. The white population of the region was relatively unaffected

One of the most interesting features of the history of Influenza A since the virus was isolated in 1933 has been the changing serological character of dominant virus strains Speaking broadly, it may be said that only in 1933 and 1934 were strains of the original WS subtype obtained. All the subsequent isolations around 1935 to 1937 from America, Australia, and Europe were quite strikingly different from WS There were many minor differences among them, but they can be regarded as conforming fairly closely to the second major serological subtype of which PR8 is the usual exemplar. In Australia in 1946, a strain CAM was isolated which proved to be serologically remote from PR8 and very close to the strains subsequently isolated during 1947 in America and Britain typified by FM1 and now often referred to as influenza virus A prime Vaccination of persons with a vaccine of PR8 did not protect against influenza of the A prime type so that the difference is one of practical importance. There are sometimes considerable divergences among strains placed in one or other of the three

major subtypes, WS, PR8, and A prime, and in our experience in Australia, there is a distinct tendency for strains of intermediate years to have intermediate serological character. The impression is gained that influenza viruses are constantly undergoing immunological change and that when a new serological subtype emerges, it tends rapidly to replace the pre-existent types in those parts of the world which are in epidemiological contact.

A strain of an influenza-like virus was isolated by Taylor (77) from a mild respiratory infection and has been studied by Hirst (78). This strain, number 1233, has characteristics which mark it off sharply from known A and B influenza viruses, and it seems not unlikely that it will eventually become influenza virus C.

The common cold.—There has been active experimental work in progess on both sides of the Atlantic, but the results obtained do not offer any hopeful indication of useful preventive measures. Andrewes (79, 80) has given a comprehensive account of four years' work with human volunteers at the Medical Research Council's unit at Salisbury. This group has found that mild but objectively recognisable colds can be produced in about 55 per cent of persons inoculated intranasally with fluid from the nose of a previous case or with suitably filtered material. Filtration studies show the virus to be smaller than that of influenza, but no more definite statement of its probable size can be given. The application of various laboratory techniques has not been fruitful, no lesions or signs of infection were observed in 17 different species of mammals experimentally inoculated, neither lesions nor evidence of multiplication (by human subinoculation) was obtained after various methods of chick embryo inoculation, and no evidence of hemagglutination could be obtained.

Topping & Atlas (81), using an American strain of virus, have been able to cultivate an agent in the allantoic cavity of the chick embryo which, on inoculation into human volunteers, produced rather severe respiratory disease 7 to 24 hr. after inoculation. Electron micrographs show particles generally similar to influenza virus but "readily distinguishable from them." A full account of this work had not appeared when this review closed.

In discussing the problem of the common cold, Andrewes lays stress on the likelihood that all volunteers obtained from normal human environments are substantially immune and only a relatively mild infection at most is produced. The "experimental animal" is, therefore, a most unsatisfactory one, and it is possible that more information may be obtainable from careful observation on isolated communities, Arctic expeditions, and the like than from experimental human infections.

All previous investigators have found no evidence of solid postinfection immunity for more than a few weeks so that nothing is known as to the existence of more than one immunological type of cold virus. Over the past year or two, there have been widespread claims that antihistaminic drugs could cure or abort the common cold. As might be expected, properly

controlled studies that have recently appeared show no benefit from the procedure (82).

Rubella in Pregnancy

Swan (83) has published a comprehensive review of the effects of rubella in pregnancy which were first brought to light by Gregg in 1941. What is probably the feature of most interest in this review is the tabulation of the various types of lesion shown by the child in terms of the month of pregnancy in which the mother suffered from rubella The essentials of several of Swan's tables are shown in Table I.

TABLE I

Incidence of Congenital Lesions According to Month of Maternal Infection*

Lesions in Children	Month of Pregnancy					Total
	1st	2nd	3rd	4th	5th and later	
Cataract	52	39	11	0	3	105
Deaf Mutism	11	83	77	35	6	212
Cardiac Lesions	65	65	35	10	5	180
Any Malformations	90	150	105	44	26	415

* Swan.

The greater likelihood of cataract following infection in the first month, and of deaf mutism in the second and third are noteworthy. A point of some interest in this respect emerges from Murray's study (84) of deafness in these children. A division of the time of maternal rubella according to weeks of pregnancy showed peaks of incidence in the first half of the second month and in the second half of the third month, perhaps corresponding to vulnerable periods in the development of the cochlea and the organ of Corti respectively.

Studies of Australian cases, now children of five and upwards, by otologists have been reported (84, 85) The average loss of hearing was 72 decibels (better ear, 65 decibels) representing moderate to severe, but not absolute, deafness.

Two recent Australian approaches toward measures for preventing rubella during pregnancy should be reported McLorinan (135) had given γ-globulin prepared from serum of donors convalescent three to six weeks after rubella to 300 pregnant women (one to four months) who had been exposed to rubella. A dose of 4 cc. was given intramuscularly as early as

possible after exposure. Six of those given serum suffered typical attacks of rubella at an appropriate period after exposure; in the other 294 no rash was reported. In November, 1949, no congenital abnormalities had been reported in the babies subsequently born that had been examined, but a relatively small proportion of the number had been reported on.

During 1948, Anderson (86) carried out a considerable series of experiments on the practicability of artificial infection of young women with active rubella virus in the form of throat washings treated with penicillin He was able to show that the virus was present in large amounts in the throat washings at the time of the rash, that it was highly infective in the form of atomized throat washings, and that it retained its infectivity for some months when frozen in dry ice. A proportion of volunteers with no history of rubella failed to be infected either by inhalation of atomized virus or by contact with fellow members of their group with typical symptoms This was taken as presumptive evidence of the relatively common occurrence of subclinical rubella It may be noted here that at least one account of subclinical rubella in a mother giving rise to severe damage in the infant has been published (85). In this incident, the father was known to have had rubella in the first month of his wife's pregnancy. She, however, was certain that she had never had a rash or symptoms suggesting german measles at any time before or during the pregnancy.

Reports continue to appear of retrospective investigations in which congenital damage observed in infants has been correlated with rubella during the first trimester of the mother's pregnancy. There is still no satisfactory study from the other direction, viz , the recognition of rubella during pregnancy and subsequent study of the fate of the fetus. English workers (87) have used the National Health Insurance records to obtain the diagnosis recorded at the time and then to follow the fate of the infant. Very little material was, however, available, and the authors' chief concern is to indicate how the answer might be obtained rather than to provide it.

Q Fever

In the literature on rickettsial disease of temperate climates and civilized communities, Q fever has occupied pride of place in the last year or two, perhaps more because of its widespread incidence and the very puzzling epidemiological features than from its intrinsic seriousness as a human disease. On the clinical side, there has been no reason to modify the description of the symptoms and course given first by Derrick (136) and elaborated by American workers in the early 1940's The wide range of severity, from completely subclinical attacks to a severe illness which may be fatal in old or debilitated persons, is frequently referred to Diagnosis is only possible by the use of appropriate laboratory tests. Complement fixation is now standard, and facilities for carrying out the test are available in most countries

As has been pointed out in a recent review by Dyer (88), the epidemiological features seem to vary considerably from one country to another. Derrick and his collaborators in Australia established a cycle involving the bandicoot (a native marsupial) as reservoir with several alternative tick vectors, and they believed that the human infections which were confined to persons in contact with cattle were due to inhalation of dried tick feces Abattoir infections analogous to those in Queensland have been reported from Texas, but in southern California what appears to be a completely different situation exists. This is dominated by the discovery that a surprisingly large proportion of dairy cattle in the Los Angeles district are excreting the rickettsia (*Coxiella burneti*) in their milk (89). In one investigation, 34 samples of pooled milk, each sample from 28 to 30 cows, were tested by guinea pig inoculation. Thirty of them were positive. When cows known to be secreting the organism are killed and examined, infection is demonstrable only in the udder and in the supramammary lymph nodes with no significant histopathological changes (90). The route by which the infection is transmitted to the dairy cows is unknown. Experimentally, the introduction of large amounts of *C. burneti* into the teat canal is followed by a brief acute mastitis with some systemic reaction. Once infection is established, it persists indefinitely (91). This is at least suggestive that infection is transmitted from one cow to another during the milking process. Another possibility is raised by Jellison *et al.* (92) in their demonstration that the spinose ear tick (*Otobius*) may be found spontaneously infected.

The recent observation of Luoto & Huebner (93) that *C. burneti* may be present in large numbers in the parturient placentae of infected cows suggests that as with *Brucella* infections, contamination of ground or herbage at parturition may be important Epidemiological studies in the Los Angeles area have shown a significant concentration of Q fever cases in people who either (*a*) work with cattle, (*b*) reside near dairies or stockyards, or (*c*) drink raw milk, 78 per cent of cases fall into one or other of these categories (94). Serological surveys of large numbers of human sera led to the same general conclusion

If one assumes that a positive complement fixation reaction indicates infection within the last five years, there is a very large yearly crop of infections in southern California. Figures by Bell *et al.* (95) gave 1.3 per cent of positive sera in the control groups not exposed to cattle or cattle products, a total of more than 5,000 sera being tested. Figures in exposed groups ranged from 11.4 per cent in workers of meat packing plants slaughtering a significant proportion of dairy cows to 20 per cent in workers handling hides and 23 per cent in dairy workers. In Texas (96), the incidence is not so high in packing house workers, but reached 8 per cent among some 1,300 employees at Fort Worth. Limited surveys of human sera in other regions of the United States (97, 98) have shown only small numbers of positive sera, again mostly from persons with some association with cattle Surveys of

cattle sera from different states are reported by Shepard (99), but the numbers are relatively small. Outside California, the only states to show more than 5 per cent of positive sera were Nebraska, Missouri, and Wisconsin.

The transfer of infection to human beings from these various bovine sources seems likely to be for the most part by inhalation of dust containing dried milk or excreta either of cattle or of their ectoparasites. The characteristic pulmonary lesions demonstrable in most severe human cases of the disease plus various types of circumstantial epidemiological evidence point strongly in this direction. *C. burneti* has been obtained from the dust of dairies and of sheep pens (100), and the circumstances of wartime infections in Italy were highly suggestive of dust infection.

The role of raw or incompletely pasteurized milk in conveying infection is not clear. Milk is heavily infected, and the *Rickettsia* is moderately heat resistant; a pasteurization plant must be working at full efficiency to ensure that the standard procedures destroy the organism (101). There is no satisfactory evidence that infected milk will produce infection by mouth, and experience in regard to laboratory infections would suggest that airborne infection from milk is quite possible. Whenever milk is poured from one receptacle to another, bubbles burst and liberate droplets into the air and heavily contaminated material could well initiate infection in this fashion. Investigation of the Q fever situation in Britain is only beginning, but there are already indications that dairy cattle are concerned in some instances (102, 103). A particularly interesting episode (103) was the infection of two pathologists and a nurse from the cadaver of a man who had died from unsuspected Q fever Histological studies of postmortem material showed that the lung tissue was loaded with enormous numbers of rickettsiae (104). This case indicates a potential source of danger to pathologists working on human material and raises the possibility that person to person infections by the respiratory route may occur In other parts of the world, Q fever seems to be associated primarily with goats Caminopetros (105) regards goats' milk as the commonest source of infection in Greece, and Bilal & Payzim (106) in Turkey found positive complement fixation reactions with sera from goats and sheep Sheep milk has been found infected in northern California (107).

It has been very interesting to watch the extension of the area known to be infected with Q fever since its first recognition in the Brisbane abattoirs in 1935 and the independent isolation of the *Rickettsia* from ticks in Montana in the following year Authentic records are now available from Australia (Queensland and South Australia), North America [California and Texas (108), especially], Panama (109), Europe [Greece (105), Italy, Switzerland (110), southern Germany (111), and England], Asia [Turkey (106), Iraq, and Indo-China] and Africa (Morocco) There seems to be no reason to believe that there has been any actual recent extension of the disease, but merely that the availability of a convenient serological test has made it

possible to sort out one more entity from the group of undiagnosable fevers It is reasonable to expect that the disease will be found in all or most regions where considerable numbers of cattle or goats are kept.

The commonest epidemiological manifestation of Q fever is the sporadic appearance of cases without evidence of case to case transmission. Occasionally, however, there are epidemic outbreaks such as the one described in Germany by Hemi & Germer (111). They observed an influenza-like illness causing 326 cases in a community of 700, the great majority occurring during the month of December, 1947. There were seven deaths, four of them in old men. This may be compared with the extraordinary epidemic among returning American servicemen described by the U S. Respiratory Diseases Commission (1947) This fairly clearly was initiated at the time the unit occupied an open-air bivouac in southern Italy, but no clue as to the mode of infection was obtained

It may be concluded that there are still some extremely interesting aspects of the ecology of Q fever to be discovered. One gets the impression of a labile microorganism, initially a typical arthropod-borne parasite, which has found it possible to adapt itself to a variety of ecological niches. The epidemiology of the human disease varies correspondingly.

The Encephalomyocarditis (EMC) Viruses

There has been considerable recent interest in a group of viruses, members of which were first encountered in the course of studies on the adaptation of poliomyelitis virus to murine hosts. It has been shown by Warren *et al.* (112) and by Dick (113) that the viruses known as M.M , Columbia-SK, encephalomyocarditis, and Mengo encephalomyelitis are immunologically closely related and produce essentially similar lesions in experimental animals In view of the characteristic occurrence of interstitial myocarditis in infected mice and guinea pigs, Warren *et al* have suggested that the viruses be referred to as the encephalomyocarditis (EMC) group.

The present significance of these viruses to human medicine is slight. Dick *et al.* (114, 115) have described an acute human infection (Mengo encephalitis) occurring in Africa and have isolated the virus from mosquitoes caught in the bush. Warren *et al.* (112) found that a group of sera from American soldiers in the Philippines who had suffered a mild "three-day fever" (in the winter of 1945 to 1946) neutralized EMC virus at significant titer. The natural habitat of the virus is uncertain, but there is increasing evidence to suggest that it may be a mosquito-borne parasite of rats, probably of more than one species Infection in rats is wholly subclinical, but large amounts of virus may be present in the tissues [Warren *et al* (116)], a circumstance suggesting that animals of this sort may be a natural reservoir.

Herpes Simplex

Anderson & Hamilton (117) have reported an interesting study of the

incidence of primary herpetic infection in an orphanage. They found that all children became infected as judged by the appearance of specific antibody, about half of them with clinical evidence of stomatitis and the other half without recognized illness. Young infants showed maternal antibody which disappeared at about six months Infection took place between 12 and 22 months of age, the insusceptibility under one year being ascribed to maternal immunity. Hayward (118) has described a complement fixation test for herpes simplex antibody which gives results in parallel with the more expensive virus neutralization test.

Infectious Hepatitis and Serum Hepatitis

The importance of serum hepatitis as a sequel to the administration of blood and blood products has stimulated work on means of preventing this complication. At the present time, ultraviolet irradiation of plasma is coming into general use as a result largely of the report by Blanchard *et al* (119). They inoculated volunteers, some with unheated icterogenic plasma, the others with the same plasma irradiated in an apparatus of the Habel-Sockrider type. In this apparatus, the plasma passes slowly in a shallow layer over the inside of a rotating glass tube which has running lengthwise down its center a cold quartz ultraviolet lamp No symptoms were observed in 11 subjects receiving irradiated plasma, while among 15 given the control material, three suffered from hepatitis with jaundice and four suffered minor illness, presumptively hepatitis.

At the same time Stokes *et al.* (120) published their results with gamma globulin used as a prophylactic measure in military hospitals on patients receiving blood or blood products. The efficacy of the measure varied according to the batch of gamma globulin (from normal human plasma pools). In one hospital, two 10 cc. injections at a 30-day interval appeared to be highly protective. In two others, a single 10 cc. dose failed to modify the incidence as compared with a control series There was an increase in the length of the incubation period, and there were no deaths as compared with four deaths in the control series It has been a general finding that gamma globulin is much less commonly responsible for serum hepatitis than other blood products This is, perhaps, to be ascribed to the concentration of antibody against serum hepatitis virus

In a paper received just as this review was being closed, Henle *et al* (121) report evidence that the virus of infectious hepatitis has been grown in chick embryos The evidence of multiplication is based on the production of an erythematous skin reaction when amniotic fluids are injected intradermally in persons who have recovered from infectious hepatitis. A laboratory test for the virus of either infectious hepatitis or serum hepatitis would be of inestimable value, and it is to be hoped that this report presages such a test. There are many possibilities of misinterpretation, however, in indirect tests of this type, and further developments should be awaited with reserve.

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Theoretical and Laboratory Studies in Virology

Work on the hemagglutinating activity of influenza and other viruses is leading to at least a preliminary understanding of the process by which some viruses gain entry to the cell. Work is farther advanced with the influenza viruses than with other groups and has been recently reviewed by Burnet (122) and Hirst (123). The virus particles make their primary attachment to receptor points which are composed essentially of mucopolysaccharide and which are present in the surface layer both of the red cell and of susceptible cells of the respiratory tract. Union is followed by enzymatic destruction of the receptor and reliberation of the virus. The nature of the enzyme concerned is not fully elucidated, but it has been shown by Burnet & Stone (124) that a functionally similar enzyme is produced by *Vibrio cholerae* This enzyme has been partially purified by Ada & French (125) and has proved a valuable reagent for theoretical studies By the administration of the vibrio enzyme, experimental animals, mice, and chick embryos can be rendered temporarily insusceptible to infection with virulent virus Within a day or two, the receptors are regenerated and susceptibility returns [Stone (126)]

Interference reactions between viruses have been recently reviewed by Henle (127). Interest in this field is growing, and it is not improbable that interpretations or applications in the clinical field will become of importance. The subclinical infection is a concept that is universally accepted as necessary for the epidemiological understanding of many virus diseases. The nature of the process by which a virus infection may be overcome rapidly and with trivial or no symptoms before the development of antibody is still obscure. Research on the nature of interference may provide a clue to its interpretation To some extent "blocking" of the receptors at the cell surface may be concerned, but recent work points strongly toward the importance of intracellular processes intimately concerned with the multiplication of virus.

Fundamental studies of the nature of the processes by which viruses multiply within the host cell are furthest advanced in the field of bacterial viruses, and a recent essay by Luria (128) should be read by all interested in the present status of this topic It is now quite certain that the infective particles which produce such characteristic images in electron micrographs do not simply invade the host bacterial cell, multiply by binary fission within its substance, and break forth as a fresh brood of virus when the bacterium lyses A variety of evidence indicates that on entering the cell, the virus particles break down into smaller units, that these enter into intimate association with the nucleoprotein and enzymatic mechanisms of the cell, and the whole activity of the cell is diverted to the synthesis of virus material Only at a relatively late stage of the process does reconstitution of infective virus particles begin. The most striking experimental evidence for this view is the production of recombinant virus. If a single bacterial cell is infected

with two or more virus particles, each of which is individually characterized by appropriate "markers," there can be found among the progeny, virus types carrying markers derived from two (or three) different "parents."

If work completed but not yet published by Burnet & Lind (129) on similar phenomena observed with influenza viruses is confirmed, these interpretations may need to be extended to viruses affecting mammalian cells The experiments involved double infections in the mouse brain of a neurotropic strain of influenza virus A and nonneurotropic strains of influenza virus of different serological subtypes. By suitable manipulations, virus strains were obtained in which the neurotropic quality, that is, the ability to multiply in the mouse brain and produce fatal encephalitis, was combined with any of three different serological characters. The original neurotropic strain had the serological character WS; the recombinants included several examples in which neurotropism was associated with each of MEL, Swine-15 and A prime serological qualities.

Closely related in this work are the recent findings of Schlesinger (130) on the fate of nonneurotropic influenza viruses injected into the mouse brain Briefly, his results indicate a single cycle of cell invasion and multiplication of virus components with liberation of what may be called fragmentary virus, detectable as hemagglutinin and complement fixing antigen, but not as infective virus. Pointing in the same direction is the finding of Hoyle (131) and the Henles (132) that influenza virus on entering susceptible cells of the chick embryo becomes undetectable for a period and that the first evidence of the infectious process taking place in the cells is the appearance of the soluble complement fixing antigen Infective virus is liberated at a later stage.

It is too early to make any dogmatic statement, but the whole trend of opinion is strongly against the view that viruses multiply intracellularly by any type of binary fission. If it is true, as Luria suggests, that in general viruses break down into very much smaller particles which, as it were, infect the whole substance of the cell and change the direction of its synthetic activity, we may well be at the beginning of a revolutionary new approach to the study of cell mechanisms

At a more immediately practical level of experimental virology special reference should be made to a series of papers summarized by Fenner (133) in which an elaborate study has been made of the experimental disease, mousepox (ectromelia). This is an infection of mice due to a virus which is physically and immunologically almost indistinguishable from the viruses of variola and vaccinia. The disease is an acute and highly infectious one which in many respects is a close analogue of human smallpox In smallpox, as in the other exanthemata, there is very little known either of the process by which infection is initiated or of the behavior of the virus during the incubation period. By careful estimation on the virus content of various organs during the course of natural and experimental mousepox, Fenner was able to present for the first time a reasonable account of these happenings in his experimental

model of an exanthematous disease. He showed that, starting with a primary lesion in some mildly traumatized skin area, there followed in succession phases of primary viremia, infection of the major blood filters of liver and spleen, a secondary viremia from these visceral sites with generalized infection of the skin, and development of a generalized rash analogous to that of smallpox. This investigation seems likely to provide the pattern for future interpretation of the human diseases. It makes it particularly desirable that more should be learned about the site and character of the initiating infection, especially in diseases like mumps and smallpox in which the virus is easily susceptible to laboratory study.

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DISEASES OF THE GASTROINTESTINAL TRACT[1]

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Recent advances in our knowledge of the nature of diseases of the gastrointestinal tract and resulting improvement of methods of therapy have occurred as a result of diligent work by physiologists, pharmacologists, pathologists, gastroenterologists, and surgeons This progress and co-operation was well evidenced by the chapter written by Eusterman & Balfour in Volume I of *Annual Review of Medicine* (146)

Although the present chapter attempts coverage of each field of special knowledge, the reader should recognize that the authors are best informed with regard to surgery. It obviously is not possible to list each reference in the several fields of work, nor is it possible to select in any way references and quotations according to merit. With the reader's permission, therefore, certain articles have been arbitrarily chosen for material or for quotations needed to develop the subjects of the chapter while other excellent studies or reviews have been omitted. An attempt is made to use the quoted references and supplementary comments toward development and presentation of current thought on gastroenterological problems. Presentation will cover consecutively the anatomical divisions of the gastrointestinal tract (esophagus, stomach and duodenum, jejunum and ileum, colon and rectum) and then the appendages (liver and biliary tract, and pancreas).

ESOPHAGUS

Dysphagia may result from functional or hysterical conditions or from neurological lesions such as bulbar palsy, amyotrophic lateral sclerosis with bulbar involvement, infantile paralysis with bulbar involvement, and myasthenia gravis. Also, dysphagia may be caused by diverticula, benign stricture, carcinoma, achalasia (often called cardiospasm), hiatus hernia, and rarely by pressure from extrinsic lesions of the neck and chest or by foreign bodies. Functional disorders are of importance to this chapter in that their diagnosis must be established only after careful study, including repeated roentgenologic and often esophagoscopic examinations, has excluded other diseases which, as with carcinoma, require prompt and specific treatment Similarly, neurological lesions are pertinent only in differential diagnosis, since treatment involves neurological methods.

Diverticula.—Diverticula of the cervical esophagus usually develop from the posterior wall of the pharynx, or occasionally from the left or right walls, and are called pulsion diverticula. As a diverticulum enlarges and descends, ingested foods and liquids are diverted through its opening into the sac, and

[1] This review covers approximately the period from January, 1947 to November, 1950.

pressure with filling intermittently obstructs the adjacent esophagus. Increasing dysphagia and loss of weight indicate surgical intervention. Lahey (1) has recommended a two-stage procedure: first, suspension or superficial placing of the sac, and second, removal. The first stage temporarily relieves symptoms but is rarely sufficient alone. However, with improvement of techniques and availability of newer chemotherapeutic agents and antibiotics Harrington (2), Sweet (3), and most surgeons today prefer a one-stage procedure, including excision of the diverticulum and primary suture of the defect. Diverticula of the lower esophagus may be of two types, traction or pulsion [Janes (4)]. In most patients, diverticula of the thoracic esophagus are asymptomatic or cause minor discomfort or obstruction. Occasionally, however, large pulsion diverticula may require suspension of the sac [Adams (5)] or removal.

Benign stricture.—Benign stricture of the esophagus usually results from swallowing of corrosive liquids, accidentally in children or with attempted suicide in adults. It may also follow regurgitation of acid digestive juices from the stomach during prolonged vomiting or infrequently may follow prolonged use of gastric or gastrointestinal suction tubes. Congenital shortening of the esophagus is emphasized by Allison (6) as a common cause of peptic ulceration and stricture of the lower esophagus. When scar tissue obstructs the lumen, producing serious dysphagia, bougie or various other esophageal dilators are used in the conventional manner and repeated dilatations accomplish relief for many patients. Some patients, however, cannot be thus treated satisfactorily. The conventional use of gastrostomy and retrograde dilatations for these patients is gradually being replaced by reconstructive procedures with or without resection of the damaged esophagus. Plastic operations for development of a tube from a cervical esophagostomy to a gastrostomy using skin of the anterior thoracic wall have been abandoned as unsatisfactory. In this country, esophagogastrostomy with resection of the lower thoracic esophagus and mobilization of the stomach up through the diaphragm, an operation originally successfully performed by Adams & Phemister (7) for carcinoma, is often employed for stricture. Allison (6), Sweet (8), and many others have used esophagogastrostomy following resection as a treatment for intractable stricture, but there is an associated appreciable operative risk. This may run as high as 25 per cent when mobilization of the stomach to the level of the clavicle or cervical esophagus is attempted. Although Rienhoff (9) succeeded in transplanting the jejunum intrathoracically in a few patients who had had esophageal resection, this procedure is not popular because of the associated great mortality risk. Probably the safest method of reconstruction of the esophagus, though currently not popular in this country, is subcutaneous mobilization of the jejunum along the chest wall to a previously fashioned cervical esophagostomy as reported by Yudin (10).

The concept that stricture of the lower esophagus may be initiated by reflux of gastric digestive juices or that, if the stricture were originally

caused by swallowing of acid or alkaline chemicals, it may be continued by this reflux process has led to two recent developments directed toward reduction of gastric acidity. Wangensteen & Leven (11) performed conventional gastric resection, removing the pylorus and the distal three-fourths of the stomach, in six patients with esophageal stricture and had satisfactory results Grimson *et al* (12) reported the use of vagotomy and gastrojejunostomy in two patients with ulcer and associated obstruction of the lower esophagus and in one patient with stricture and esophagitis. Satisfactory relief of symptoms and opening of the area of the stricture followed either type of operation. It seems probable that gastroenterostomy should be part of either operation since each procedure includes division of the vagus nerves, which often causes dysfunction of the denervated pylorus with gastric retention and upward regurgitation of gastric juices. Additional evidence favoring use of resection or of vagotomy in patients with strictures of the lower esophagus is afforded by the experiments of Topete *et al.* (13) which demonstrate in dogs that gastroesophageal anastomosis without vagotomy is frequently followed by esophagitis, ulcer, and stricture, and that these complications do not occur when esophagogastrostomy is performed with vagotomy. Additional evidence is included in the studies of Ripley *et al.* (14), who produced esophageal stricture in dogs and then performed extensive resections of the stomach following which the course of the stricture was favorably modified.

Currently, we have been using Banthine in lieu of surgery for certain patients with esophageal stricture and have had encouraging results In view of the evidence that peptic digestive juices can cause or aggravate lower esophageal stricture, it does seem indicated that conventional antacid and dietary medical management plus the use of an anticholinergic drug would be of primary importance in treatment of these lesions.

Carcinoma.—Successful treatment of carcinoma of the esophagus depends upon early recognition and prompt surgical intervention. Roentgenologic findings suggesting malignancy can usually be confirmed by esophagoscopy and biopsy. Use of radium or roentgen ray therapy is generally considered ineffective Operations are resection of the thoracic esophagus, leaving cervical esophagostomy and abdominal gastrostomy as performed by Torek (15), or resection of the lower esophagus and often of the middle or mid and upper thoracic esophagus, restoring continuity by esophagogastrostomy [Adams & Phemister (7)] Advantages of the Torek procedure are low operative risk and the facility with which lesions of the mid and upper thoracic esophagus can be removed. Disadvantages are difficulties in the use of the gastrostomy by some patients, since dysfunction of the pyloric sphincter resulting from the associated vagotomy may cause gastric retention, leak of gastric juice around the gastrostomy tube, and even gastritis with bleeding unless a secondary gastroenterostomy is added Also, a small dressing must be worn over the esophagostomy opening. Restoration of continuity between the pharynx and the intestinal tract requires recon-

struction of an esophagus as described above under stricture. This is only done at such a time as the patient may have survived the likelihood of immediate recurrence of tumor.

Advantages of the resection and primary esophagogastrostomy are that the patient may swallow soon after operation. Nevertheless, these patients also have retention occasionally (because of the associated vagotomy) and bleeding infrequently. Disadvantages of resection with esophagogastrostomy center largely around the increased magnitude of this operation, the risk of leak at the anastomosis site, the increased operative mortality rate, and limited excision of the tumor, since often there is a narrow margin between the available site for transection of the esophagus and the location of the tumor. Five-year survivals after either operation are infrequent, for most patients have extension of the tumor at the time of operation and develop recurrence afterward. The reviewers are among the few surgeons who now prefer the Torek procedure for carcinoma of the mid and upper thoracic esophagus. Sweet (16), Garlock (17), and many others prefer resection and high mobilization of the stomach with esophagogastrostomy for lesions in this area All are in agreement that the operation of Adams & Phemister (7) is preferable for lesions of the lower third of the esophagus.

Achalasia.—Dysfunction of the sphincter between the esophagus and the stomach or of the sphincter and a short segment of the lower esophagus causes dysphagia and enlargement of the thoracic esophagus (megaesophagus) or enlargement with lengthening and kinking (dolichoesophagus). Wolf & Almy (18), Alvarez (19), and many other authors term this condition cardiospasm. Nevertheless, they describe dysfunction of peristalsis in the lower segment, and Alvarez in particular emphasizes absence of ganglion cells at the point of apparent obstruction The reviewers prefer the term achalasia, which evidently was originated in Guy's Hospital in London around 1913 when Hurst (20) demonstrated that a rubber tube filled with mercury could be dropped through the esophagus into the stomach and withdrawn without meeting spasm or other appreciable resistance. Other evidence against spasm of the sphincter as a cause of this condition has been presented [Grimson *et al* (21)] The reviewers also attributed the enlargement of the esophagus above the point of dysfunction to dilatation by food retained because of obstruction, since frequently the dilated portion of the esophagus gradually resumes normal size during the first year or two after an esophagogastrostomy which affords adequate drainage. Alvarez (19) has reviewed the evidence favoring partial or complete destruction of the myenteric plexus and he and Wolf (18) have outlined the subsidiary importance of emotional factors.

Medical management consists of advice with regard to rest and relaxation and use of sedatives. Alternately tried are parasympathomimetic and parasympatholytic agents. Dilatation of the cardiac sphincter or lower esophagus by mechanical devices, a procedure originally recommended by Plummer (22), is commonly employed and frequently affords intervals of improvement. Many patients, however, experience progressive dysphagia and dilata-

tion of the esophagus and, because of progressive loss of weight or development of esophagitis with bleeding, require surgery. Of the several operations designed to drain the esophagus, the procedure of Grondahl (23), transabdominal esophagogastrostomy using a technique similar to that of the Finney gastroduodenostomy, is most frequently employed in this country. Relief of symptoms is usually achieved. However, late after operation many patients develop esophagitis, stricture, or ulcer. For the reasons described in the preceding paragraph on stricture, we have now combined cardioplasty with vagotomy and gastroenterostomy in three patients, and Adams (13) has performed this operation in another. Wangensteen (24) has performed esophagogastrostomy following resection of the lower esophagus and sphincter and the upper stomach in five patients and reports good results This operation also includes division of the vagus nerves at the time of esophageal resection. It seems apparent that achalasia patients formerly treated by esophagogastrostomy without vagotomy or resection or now treated by this procedure should receive postoperative medical management directed toward reduction of acidity of their gastric juice.

Hiatus hernia.—Herniation of a portion of the fundus of the stomach up through the hiatus of the diaphragm, whether or not associated with a congenitally short esophagus, can cause dysphagia, sensations of substernal pressure particularly when bending or stooping, and epigastric distress. Differential diagnosis should exclude coronary heart disease, peptic ulcer, and cholecystitis Richards & Crockett (25) summarize experiences in 24 typical cases, and Brick (26) reports on 308 cases, each series being collected within a two-year period. Master *et al.* (27) made an intensive review of the cardiac status in 57 consecutive patients and also carefully reviewed the literature They state that 15 of these patients had purely gastrointestinal symptoms, 29 both gastrointestinal and cardiac complaints, 3 only cardiac complaints and 10 symptoms attributable to anemia secondary to hemorrhage They emphasize that hiatus hernia and coronary artery disease may coexist

Vincent (28) studied 21 patients with the paraesophageal type of hernia 110 with congenital shortening of the esophagus, and 16 with a short esophagus and a portion of the stomach above the diaphragm, but with stricture between the esophagus and the herniated stomach They state that occurrence of these conditions is not infrequent.

A roentgenologic diagnosis of hiatus hernia is often made in patients who describe no symptoms Frequently, however, the hernia has produced symptoms. In this event, medical therapy usually consists of recommending an ulcer type of diet, use of antacids, prescription of antispasmodic or atropine-series drugs, and reduction of weight for those patients who are obese. Use of β-diethylaminoethylxanthene-9-carboxylate-methobromide (Banthine) in two patients in our series has relieved symptoms. Occasionally surgery may be necessary. The older operation was transabdominal repair. Lately, a transthoracic supradiaphragmatic approach has been preferred by many surgeons In view of the not infrequent recurrence of herniation following either procedure, we prefer a transthoracic approach with an associated in-

cision through the diaphragm so that repair can be both infradiaphragmatic and supradiaphragmatic. For older patients or those with cardiac or other diseases which preclude major operation, Morton (29) is usually credited with introduction of a simpler procedure, the crushing or division of the left phrenic nerve. This may afford complete or partial relief It is our hope that the number of patients requiring surgery for hiatus hernia will be reduced as Banthine or other anticholinergic drugs may diminish gastric secretions and motility and thus lessen peptic digestion of the intrathoracic stomach and the lower esophagus.

Varices of the lower esophagus will not be discussed in this section since they are part of the problem of portal hypertension and cirrhosis to be discussed under liver.

STOMACH AND DUODENUM

Ulcerative Diseases

Diseases of the stomach and duodenum have been the subject of many excellent studies and reports during the last few years. In general, the reports deal with peptic ulcer or related conditions which will now be discussed and with neoplastic diseases which will be discussed subsequently.

Gastric ulcer differs from duodenal ulcer primarily in respect to its tendency to be associated with malignancy or possibly to eventually develop malignant degeneration. Lahey (30) recommends that a diagnosis of gastric ulcer warrants subtotal or total gastrectomy. Most gastroenterologists and surgeons, however, recognize that healing of gastric ulcer can be achieved in some patients and recommend trial of medical management. Dragstedt *et al.* (31) and Lyons & Grimson (32) recommend that although readily resectable intractable ulcer of the antrum or mid portion of the stomach should be removed by subtotal gastric resection, relatively inaccessible juxta-esophageal ulcer should be treated by vagotomy with gastroenterostomy, thus reserving total gastrectomy or radical tumor operation for those patients with juxta-esophageal lesions which fail to heal during a few months and apparently are malignant Similarly, resection of the distal half or three-quarters of the stomach without removal of the juxta-esophageal gastric ulcer has been recommended by Colp & Druckerman (33). With the exception of the risk of malignancy, there seems little need to differentiate gastric ulcer from esophageal ulcer, jejunal ulcer following gastroenterostomy or resection, and duodenal ulcer. Accordingly for the remainder of this review, and for convenience of the reader, ulcers of these four varieties will be grouped under the general term peptic ulcer.

Etiology of peptic ulcer.—Although the etiology of peptic ulcer is commonly considered unknown, many believe that the main factors are known and rather well understood The reader is referred to the excellent review by Mayo (34) for detailed discussion and bibliography. In general, gastric hypermotility and hyperacidity are considered the two main factors causing ulcer. Secondary factors, however, may be important Meyer *et al* (35) suggest that increase in amount or activity of the mucolytic enzyme, lysozyme,

may play a role in the pathogenesis of ulcer. Wolf (36) emphasizes hyperemia or turgescence of the gastric mucosa as a factor favoring development of ulcer. He states that this occurs as a psychosomatic process during conditions such as repressed anger or rage and is mediated through the vagus nerves Other vasomotor abnormalities, such as spasm, arteriosclerosis, thrombosis, or embolism of vessels at the ulcer site, are thought important as a result of autopsy studies of multiple acute ulcerations occurring in moribund patients. Baronofsky & Wangensteen (37) produced ulcer experimentally by the intravenous injection of small amounts of fat. Streptococci or some other bacteria reaching the area of ulceration with swallowed food or as a mycotic embolus were thought important by Rosenow (38)

Undoubtedly acute ulcers may arise from various causes Occasionally, they may effect sudden perforation or hemorrhage. Many individuals describe ulcer-like symptoms for a few days or weeks and then experience relief with or without medical diagnosis and advice Others have occasional recurrences and greater difficulty requiring medical management. Still others have frequent recurrences and, at times, intractable symptoms.

The main clinical problem in ulcer is the cause of frequent recurrences or of intractability. Levin and co-workers (39) determined that the average volume of secretions during the 12 night hours was 581 cc. in normal subjects and 1,004 cc. in patients with duodenal ulcer. Peristalsis was often hyperactive in ulcer patients preceding vagotomy [Grimson *et al.* (40)] Hyperacidity and hypermotility not only are present before the development of ulcer, but also persist during the intervals of quiescence between recurrences This persistance of hyperacidity and hypermotility is commonly considered an important contributing factor responsible for reactivation of ulcer or development of intractability. However, clinical experiences with vagotomy (40) and with Banthine (41) have led the reviewers to believe that development of obstruction by scar tissue or by abnormal function of the ejection cycle of the pylorus and sphincter may be an important mechanical factor contributing toward chronicity of ulcer in some patients.

The roles which the humoral mechanism of the antrum of the stomach, gastrin, and the neurogenic mechanism, vagus, play separately or cooperatively in the development of ulcer have been well demonstrated by Dragstedt and associates (42) during a series of experiments studying acidity in dogs. Results indicate that the vagus is important Wangensteen (43) emphasizes the chemical aspects of ulcer, and he and his associates have performed many experiments inducing ulcer by injecting histamine in beeswax into dogs. As a result of studies by these and many other investigators and as a result of clinical observation and testing of patients, it is evident that humoral and neurogenic mechanisms causing hypermotility and hyperacidity are each important.

Medical management of peptic ulcer.—Since the days of the Sippy diet, medical management of patients with peptic ulcer has been directed toward neutralization of acid by the use of powders, gels, resins, etc., and by the use of frequent feedings of neutralizing foods. Atropine and drugs of the atropine

series have been employed for reduction of acidity or spasm, though effects are inconsistent. Also, psychosomatic factors have been considered, and rest and relaxation recommended. Gastroenterologists attribute various emphases to each of the above factors. The greatest change in the medical management of ulcer during the last year seems to have been in the field of pharmacology. *Most physicians currently are using Banthine as a supplement to diet, antacids, and a general rest program or occasionally in lieu of this medical program.*

Banthine is a curare-form drug with a marked and long lasting anticholinergic property The drug in small doses, 50 to 100 mg., selectively blocks the parasympathetic nervous system. Hambourger *et al* (44) have recently reviewed its pharmacology. Moderately large doses block the autonomic ganglia and apparently the ganglia of the myenteric plexus. After completing studies in dogs, it was the privilege of Chittum *et al.* (45), in January of 1949, to first test Banthine in human patients. They observed [Longino *et al.* (46)] consistent reduction of motility and usually a decrease in volume and acidity of gastric secretions following parenteral or oral administration of the drug, and they compared [Lyons *et al.* (47)] the secretory and motor effects of Banthine with those of dibutylurethane of dimethylethylammonium sulfate (Dibutoline) and atropine, and also studied the change in the secretory response to insulin-induced hypoglycemia. Banthine given parenterally reduced acidity more consistently and for longer periods of time than did Dibutoline or atropine Reduction of motility occurred regularly with Banthine and Dibutoline and less consistently with atropine Reduction of acidity and motility following Banthine given parenterally lasted 2½ to 4½ hr. When given orally, Dibutoline was ineffective and atropine poorly effective, but Banthine was as effective as it has been when given parenterally. Banthine in amounts of 200 mg. given 1 hr. before intravenous administration of 20 units of insulin prevented hypersecretion during the hour of hypoglycemia in most patients, though hypersecretion occurred in some during the second hour after insulin and the third hour after Banthine. In an occasional patient, Banthine prevented the hypersecretion response to insulin induced hypoglycemia during an entire four-hour period of observation. In March of 1949, the treatment of ulcer patients with Banthine was initiated [Grimson *et al* (48)]. Results were most encouraging

Surgical management of peptic ulcer—The conventional indications for use of surgery in patients with ulcer resistant to medical treatment have been: suspicion of malignancy as with gastric ulcer, occurrence of one or more massive hemorrhages, development of obstruction and persistence of pain, or inability to follow a regular diet or medical program Emergency surgery is indicated for acute perforation and also for some patients with exsanguinating hemorrhage after it has been determined that bleeding will not stop with conservative treatment There seems to be general agreement among surgeons that persistent gastric ulcer, if located in the distal two-thirds of the stomach and readily accessible, should be treated by subtotal resection because of risk of malignancy.

Operation for patients who have had one or more massive hemorrhages

from duodenal ulcer may be either vagotomy with gastroenterostomy or subtotal gastric resection. Reports by Lahey (30) and others indicate that recurrence of bleeding in these patients when treated by resection is high; whereas, reports by Dragstedt *et al.* (49), Grimson *et al.* (40), and Crile *et al.* (50) demonstrate that massive hemorrhage after complete vagotomy and gastroenterostomy rarely occurs Accordingly, it would seem to be logical that regardless of any preference of one or the other operative procedure, patients who have had repeated hemorrhages should be treated by vagotomy and gastroenterostomy. For patients with persistent obstruction or pain and for those having incapacitating symptoms because of inability to follow a regular diet and medical program, most surgeons [Glenn & Harrison (51)] still continue using subtotal gastric resection, though a growing minority of surgeons experienced in use of vagotomy with gastroenterostomy and with management of the occasionally troublesome side effects of denervation, prefer this procedure. Lyons & Grimson (32), after comparing results in a contemporary five-year series of 132 resections and 135 vagotomies, found that mortality rate and incidence of recurrence of ulcer was higher following resection than following vagotomy with gastroenterostomy, and that incidence of satisfactory results as well as incidence of disappointing results were approximately equal in the two groups It was recommended that regardless of preference, surgeons might employ vagotomy and gastroenterostomy rather than resection when indurated or extensively scarred duodenal ulcers were found at operation, for it was under these circumstances that attempts to remove or exclude the ulcer were followed by a high incidence of operative complications. Because of the not infrequent occurrence of side effects or disappointing results following either resection or vagotomy and gastroenterostomy, the reviewers are encouraged [Grimson, Lyons & Flowe (41)] that preliminary results of use of Banthine in lieu of surgery in 62 patients meeting indication for operation suggest that the number of patients requiring surgery may be reduced. Only 10 of these patients have as yet required operation, and each of the 10 had marked obstruction.

Emergency surgery for acute perforation of a peptic ulcer usually consists of closure by simple suture Risk of operation is low if diagnosis and treatment are executed during the first few hours [Mayo & Fitchett (52)] There is as yet variation of opinion concerning the time when emergency surgery should be performed for exsanguinating hemorrhage, though, as described by Gardner & Hart (53), the operation used should be subtotal gastrectomy with removal of the ulcer or control of the bleeding point Stewart *et al* (54) are among those who favor early gastric resection for acute massive hemorrhage, whereas Bowers & Rossett (55) are among those who favor conservatism.

Moore *et al.* (56) have reviewed the follow-up course of 1,080 patients with peptic ulcer treated either medically or surgically between 1942 and 1946, and they conclude that following conventional surgery, only half as many patients have had unsatisfactory results with regard to symptoms and rehabilitation as occurred among those managed without operation

As one studies the results of medical or surgical management of peptic

ulcer, one is impressed not only by the high incidence of good results but also by the relatively high incidence of disappointing results. It seems obvious that improvement of methods of treatment is necessary. One improvement would be early and continuous use of a simple therapeutic program which patients can and will follow. This could prevent development of obstruction by scar tissue or of other complications which would lead to surgery. The continuing program should control hypermotility and hyperacidity during the night hours as well as during the day. It is hoped that the development and use of Banthine or of other new selectively acting anticholinergic or parasympatholytic drugs may aid toward the development of such a program and that patients with ulcer may more frequently be spared the occurrence of complications

Neoplastic Diseases of the Stomach

Of the benign and malignant lesions occurring in the stomach, carcinoma is by far the most common. Cause of carcinoma or of other neoplasms is not *definitely known. Successful treatment of tumors of the stomach depends* upon early diagnosis and operation. Symptoms are variable, and unfortunately, many malignant lesions are inoperable when a patient first presents himself for examination. Cancer societies are conducting routine roentgen ray surveys to determine whether a significant number of lesions can be detected to warrant routine diagnostic studies. Also, physicians are emphasizing that careful prophylactic care should be used in treatment of lesions such as gastric polyp or gastric ulcer which are associated with some risk of malignancy. Certainly careful attention to patients with symptoms of upper abdominal discomfort, loss of weight, or anemia is indicated, and this, with use of radiographic techniques or gastroscopy when indicated, is presently the most important approach to early diagnosis and treatment.

Carcinoma of the stomach.—Two new approaches to the diagnosis of carcinoma of the stomach are under investigation. One deals with Papanicolaou cytologic techniques applied to gastric washings. Ulfelder *et al.* (57), Swarts *et al* (58), and others indicate that this method is helpful when the cytologic diagnosis is positive but is of little value when it is negative The other method of diagnosis deals with measurement of potential difference across the human gastric membranes [Goodman (59), Sawyer *et al.* (60), and Ravin *et al.* (61)]. A characteristic alteration of the normal response to stimuli such as a test meal occurs as judged by measurements of electropotentials in 85 per cent or more of the patients with malignant lesions.

Operations for carcinoma of the stomach vary from subtotal resection to total gastrectomy and frequently include removal of the omentum and of all accessible nodes Invasion into adjacent viscera such as pancreas, liver, and colon may necessitate extension of operation to include parts of these organs and, if necessary, the spleen. Resection of carcinoma of the upper stomach is often accomplished through a transthoracic approach or through a thoracoabdominal incision. Lahey & Marshall (62), Wangensteen (63), and many others have contributed techniques which facilitate use of resection to in-

clude patients formerly considered inoperable and extension of surgery for less advanced lesions in the hope of increasing the percentage of five year survivals. Also, more and more frequently, secondary operations for resection of localized areas of recurrence are undertaken. Though the percentage of patients surviving five years or more after resection of carcinoma has slowly increased, the unfortunate fact remains that whichever statistics are considered, more than three-quarters of the patients with carcinoma of the stomach die of the disease.

Sarcoma of the stomach —Thompson & Oyster (64), in an excellent review of gastric neoplasms other than carcinoma, describe the incidence of sarcoma as ranging from 1 to 2 per cent of all tumors of the stomach. Most frequent are the lymphosarcomas and less frequent the fibrosarcomas and myosarcomas Treatment is surgical removal. Irradiation may be employed as a treatment for selected patients if the lesion cannot be removed, it may be used as an adjunct to surgery, and it is particularly effective in aiding control of lymphosarcoma.

Benign lesions of the stomach.—Thompson & Oyster (64) quote varying incidences of occurrence of benign lesions, different authors describing occurrence in less than 1 per cent or as much as 23.2 per cent. The reports describing the lowest incidence are based on routine necropsy observations, and those describing the highest are based upon material collected by surgical pathologists. Eliason & Wright (65) and Minnes & Geschickter (66) have each collected large groups of benign tumors Approximately half of the benign lesions are leiomyomas. Next in instance are polyps, neurofibromas, papillomas, and adenomas. Fibromas and lipomas constitute about 5 per cent of the tumors, and occurrence of polyposis is less than 2 per cent. Other mesenchymal and endothelial lesions occur infrequently as do cysts. Of these lesions, the epithelial group including polyps are of greatest concern as possible precursors to malignancy. Small, apparently benign tumors encountered during operation often turn out to be areas of aberrant pancreas rather than true neoplasms.

Neoplastic Diseases of the Duodenum

Neoplasms of the duodenum are relatively rare For practical purposes, the possibility of carcinoma can be dismissed from the differential diagnosis in patients with duodenal ulcer. Ewing (67) quotes authors listing the incidence of carcinoma of the entire duodenum as only 4 per cent of all intestinal carcinomas. Carcinomas reported rarely followed duodenal ulcer, occasionally occurred in the third portion of the duodenum, and more commonly occurred in the second portion of the duodenum and in or about the biliary papilla. Neoplasms of the duodenum other than carcinoma occur infrequently. They are similar in type to those occurring elsewhere in the small intestine.

Lesions of the biliary papilla are often readily recognizable roentgenologically as filling defects and, when diagnosed during operation as malignant, are best treated by pancreaticoduodenectomy. When benign, these lesions may be excised locally, reimplanting the biliary and pancreatic ducts.

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Diverticula of the stomach.—Thin walled diverticula arising from the fundus of the stomach near the esophageal hiatus constitute an interesting though rare condition Symptoms may resemble those of peptic ulcer. Walters (73) discusses clinical and roentgenologic aspects in five patients. The reviewers' single patient with this lesion has been completely relieved of typical ulcer symptoms following excision of the diverticulum and repair. At operation, no associated ulcer was found.

Diverticula of the duodenum.—Diverticula of the duodenum usually occur in its second or third portion and are relatively easily and frequently diagnosed roentgenologically. Often their presence is detected incidental to roentgen ray study in patients with duodenal ulcer At other times, they are detected during routine gastrointestinal examinations In either event, the diverticula themselves seldom produce symptoms and seldom need be removed. A recent report by Dunstan *et al* (74) presents observations comparable to those in numerous other reports. Of their 32 patients, 4 had complications requiring surgery. It is of interest that incidental findings at operation were leiomyosarcoma in one patient, leiomyoma in another, and an ulcer in the diverticulum in a third. Surgical repair when necessary should be carried out with great care that injury to the common bile duct be avoided, for this duct may be closely incorporated in the wall of the sac.

JEJUNUM AND ILEUM

The jejunum and ileum are a most important part of the gastrointestinal tract since extensive damage by disease or removal by surgery creates a serious nutritional problem. Also, the small intestine may be responsible for a variety of otherwise unexplained visceral pain problems Recognition of abnormalities or diseases is aided by use of roentgenologic techniques which record the transit time of barium as well as outlining caliber and mucosal pattern Methods of intubation of the jejunum and ileum using long suction tubes [Miller & Abbott (75)] or multiple balloons [Chapman *et al.* (76)] have further aided study.

Enteritis.—Regional enteritis involves one or more areas of the small intestine, and terminal ileitis involves the terminal ileum and occasionally extends into the cecum Etiology of either condition is as yet unknown. Prognosis is often serious Kiefer, Marshall & Brolsma (77), Hawthorne & Frobese (78), and Chess *et al.* (79) have summarized experiences representative of current thought. Acute enteritis may produce signs of an acute abdomen leading to exploration It is generally recommended that acutely inflamed segments thus encountered be not resected Chronic terminal enteritis, however, may require surgery because of discomfort, diarrhea, weight loss, or the occurrence of obstruction and fistulae. Usual treatment is exclusion in preference to the older practice of resection because the risk of operation with exclusion is low and some have stated that recurrence is less frequent. Regional enteritis may be treated by resection of the involved segments by enteroenterostomy around the involved segments or, as is the reviewers'

Miscellaneous Diseases of the Stomach and Duodenum

Prolapse of gastric mucosa.—Herniation of redundant rugal folds of gastric mucosa through the pyloric sphincter is being recognized with increasing frequency and can cause pain, vomiting, and hemorrhage. Ferguson (68) suggests that the etiologic factor is basically inflammatory, leading to hypertrophy and then to prolapse. Zacho (69) emphasizes that prolapse may be due to a pedunculated tumor and states that prior to 1945, only 23 cases had been reported in which the condition was caused solely by redundance and laxness of the mucosa of the pyloric region. Bralow *et al.* (70) report coexistence of duodenal ulcer and prolapse in three patients. Although duodenal ulcer is rarely associated with prolapse, the occurrence of ulcer-like symptoms is frequent.

Most patients respond to conventional ulcer management, and the reviewers have one patient with a large prolapse and with pain intractable to conventional medical management who has been completely relieved by continuing use of Banthine. Patients have been treated surgically using pyloroplasty to open the pyloric sphincter. One of these patients, two years after relief by pyloroplasty, developed ulcer-like symptoms requiring temporary use of Banthine. Although result of pyloroplasty in others has been satisfactory, the reviewers question whether this operation will be the procedure of choice as further experiences accumulate. Certainly, it is evident that careful study by roentgenologists has discovered this condition in many patients who otherwise would have been considered as having a functional distress problem.

Chronic gastritis.—Chronic gastritis remains a disease of undetermined etiology. Findley and associates (71) studied 50 patients with atrophy of the gastric mucosa, 50 with superficial gastritis, 50 with hypertrophic gastritis, and 100 with apparently normal gastric mucosa. They described the predominant complaint of the gastritis patients as epigastric pain which continued with little variation and with no definite relationship to the taking of meals. Milder distress, when present, had no characteristic pattern. Histamine tests produced the smallest amounts of acid in the group with mucosal atrophy and a somewhat higher amount among patients with superficial gastritis. Responses in patients with hypertrophic gastritis more closely approximated those in the control group. Histamine anacidity occurred frequently among the group with atrophic gastritis and not infrequently among the patients with superficial gastritis. Even in those with hypertrophic gastritis, the incidence of anacidity was more frequent than among the controls.

Miller *et al.* (72) used various chemical and physical agents to damage explanted fundic mucosa of dogs, and they demonstrated progressive regeneration of mucosa and gradual return of function. Treatment of patients with gastritis remains an individual problem, but limitation of diet is em- [illegible] has been reported to be of benefit in patients with *superficial* [illegible]stritis. Benefit also occurs with use [illegible]e, described above

mortality rate has improved only slightly over the years despite advances in therapeutic methods.

Neoplasms of the small intestine.—Brown & Nalefski (85) state that approximately 300 proven cases of carcinoma of the small bowel are all that had been reported by 1950. In their experience, carcinoma of the small bowel did not produce any characteristic clinical symptoms, and they believe that diagnosis in the early stages must be made by exclusion. Sarcomas are somewhat less frequent than carcinomas. Treatment is removal if the diagnosis is suspected or is made during exploratory operation. Also, any of the other malignancies related to the structures of the gut and its nerves and blood vessels may occur in the small intestine. Certain developmental faults may give rise to duplication of the gut and formation of enteric cysts.

COLON AND RECTUM

The literature on colon and rectum is voluminous Diseases and tumors comprise a major part of the field of gastroenterology and surgery. Comments on the several aspects of diseases of the colon and rectum will be necessarily brief, and acknowledgments by reference few.

Inflammatory Diseases of the Colon and Rectum

Ulcerative colitis —Nonspecific ulcerative colitis remains a serious clinical problem in spite of many new methods of therapy. That emotional tension can adversely affect function of the colon is generally accepted and has been confirmed by Almy *et al.* (86) as a result of kymographic studies of motility of the sigmoid. Mahoney *et al.* (87) state that patients suffering with ulcerative colitis are complex neurotics but that none of the personality traits observed are specific for the disease. Wener & Polonsky (88) are of the opinion that hyperemia, engorgement, edema, and trauma from vigorous contractions of the colon resulting from emotional stress may be important factors in the pathogenesis of human ulcerative colitis. Evidently sympathetic, parasympathetic, or mixed responses may occur

It is evident that therapy should include attention to emotional problems and some effort toward blocking of the efferent pathways of the autonomic nervous system. Studies of the action of Banthine on the colon by Kern & Almy (89) indicate that the drug reduces or abolishes colonic activity and decreases or blocks the gastrocolic reflex occurring with ingestion of 200 cc. of milk. Banthine has been used for patients with ulcerative colitis, but results have only occasionally been encouraging. Dennis *et al* (90), recognizing that parasympathetic impulses through the vagus probably reach only the right colon, nevertheless performed vagotomy in patients with ulcerative colitis and noticed some benefit They considered the mechanism involved as unsettled and suggested reduction in tone of the colon, interruption of gastrocolic reflex, decrease in the intestinal juices, delay of transit of food with slow emptying of the stomach or possibly change in lysozyme activity as explanations for benefit.

Much work has been done in bacteriology of ulcerative colitis and use of

preference, by exclusion using the Roux technique and leaving the involved segment with its proximal end closed. Careful attention must be paid to preserving as much as possible of the intestine, for radical resection does not reduce rate of recurrences. Also, extension of the disease and need for subsequent operation combine in some patients to shorten the gut and decrease its function until serious malnutrition occurs. Kiefer, Marshall & Brolsma (77) recommend medical management for patients with localized disease of short duration and for those with uncomplicated but widespread disease involving so much of the intestine that removal would seriously impair absorption. Medical management is nonspecific and includes rest, supportive nutrition, correction of anemia and hypoproteinemia, use of drugs to decrease intestinal activity, and use of chemotherapy or antibiotics to control infection.

Diverticula.—Diverticula of the small intestine may be single, but are usually multiple. Occasionally, these may become inflamed, producing diverticulitis [Fox *et al.* (80)]. Other symptoms are bleeding, pain, or obstruction. One or a few diverticula can be readily removed surgically. Multiple diverticula offer a more difficult problem. Fiske & Asher (81) report a patient with multiple diverticula of the stomach, duodenum, jejunum, ileum, bladder, and urethra.

Meckel's diverticulum.—The presence of a congenital Meckel's diverticulum is suspected in any patient with unexplained gastrointestinal bleeding, obstruction, or peritoneal irritation Owen & Finney (82) describe experiences with 143 patients in whom the diagnosis of Meckel's diverticulum was verified. Gastric mucosa was present in 33, duodenal mucosa in 3, pancreatic tissue in 2, and colonic mucosa in 1. In 16 patients, an ulcer was found. There were 11 instances of perforation. Passage of fresh blood by rectum was the most common symptom. Not uncommonly, a Meckel's diverticulum is associated with adhesions or bands producing obstruction of loops of adjacent bowel. Disease of Meckel's diverticulum indicates its removal.

Obstruction.—The development of intubation decompression methods for treating obstruction of the small intestine caused by multiple adhesions has been previously reviewed [Grimson & Hodge (83)]. Single or repeated episodes of obstruction caused by an inflammatory process or by adhesions can usually be treated by suction decompression without surgery, providing symptoms of an acute abdomen suggesting strangulation of gut do not occur and providing a probable diagnosis of adhesions as a cause of obstruction can be made. It is conventional practice to defer surgery only 48 hr. during trial of intubation decompression, performing exploration or simple enterostomy if relief is not obtained during this time.

Obstruction of the small intestine other than that caused by adhesive or inflammatory processes is usually associated with signs of an acute abdomen and risk of strangulation of bowel. Surgical attention should be prompt. Coller & Buxton (84) review experiences with 198 cases and emphasize risk of delay of operation. They recommend use of suction and correction of dehydration and shock as important adjuncts to surgery but note that the

population of the United States is infected with *Endamoeba histolytica* and that 5 to 10 per cent of these develop lesions of surgical significance such as appendicitis, perforation of the bowel, amebic granuloma (ameboma), stenosis, or pseudopolyposis Many also developed infections elsewhere, particularly hepatic abscess. Administration of emetine is the classical treatment, though other drugs are effective; and McVay, Laird & Sprunt (100) report successful use of aureomycin.

Granulomas of the rectum —Adams *et al* (101) emphasize the occurrence of stricture in patients with lymphogranuloma and describe improvement and an average weight gain of 30 lb. in 45 patients followed two or more years after surgical resection of the lesion. Tuberculous fistulae of the rectum of 13 patients were described by Knapp (102), and excision plus the use of streptomycin was employed successfully

NEOPLASTIC DISEASES OF THE COLON AND RECTUM

Carcinoma.—Carcinoma of the large bowel and rectum is now more frequently diagnosed in an early stage, as the importance of careful digital and proctoscopic examination of the rectum and lower sigmoid and of roentgenologic examination of the upper colon is emphasized by numerous medical and lay authors Change of bowel habit and appearance of blood in the stools are well recognized early signs. The occurrence of abdominal pain or mass is usually a late sign Buser, Kirsner & Palmer (103) report 478 cases and emphasize that, of these, the tumor was within reach of a proctoscope in 276 Pain was the most frequent symptom with rectal bleeding next. Weight loss and anemia were frequent associated findings

Surgeons report a variety of techniques for resection. In general, improved methods of preparation, including use of antibiotics and the development of transverse or oblique incisions, have aided the practice of more radical resection of bowel and mesentery for lesions of the colon and upper sigmoid and more frequent primary restoration of intestinal continuity by direct anastomosis Combined abdominal-perineal resection with permanent colostomy is usually the procedure of choice for lesions of the lower sigmoid and rectum In selected patients, the sphincter-saving or pull-through operations are employed by Bacon (104) and others If the pull-through operation is properly performed for patients with appropriately located small lesions, the area of resection can be wide and function of the sphincter excellent. David & Gilchrist (105), using the combined abdominal-perineal resection for carcinoma of the lower sigmoid and rectum, found that 51 per cent of those patients with the lesion located below the peritoneal reflection and 65 per cent with lesions above this level but in the lower sigmoid were free of disease after five years Postlethwait (106) describes a five-year survival rate of 57 per cent for patients with lesions of the rectum, a rate of 50 per cent for lesions of the sigmoid and transverse colon, and somewhat lower rates for lesions elsewhere in the large bowel.

Polyps—Rankin (107), Cattell (108), and Buie *et al* (109), reviewing the problem of treatment of polyps of the colon and rectum, emphasized that

chemotherapy and antibiotics. Seneca & Henderson (91) have made a recent study and found that the total intestinal bacteria count is increased 85-fold while the coliform bacteria count is increased 50-fold over that of the normal. They believe that the marked increase in bacteria and in enzymatic activity of these bacteria leads to invasion and infection of the mucous membrane. Bercovitz (92), Marshall, Palmer & Kirsner (93), and several others have reviewed the problem of use of chemotherapy or of antibiotics and emphasized that these agents are often valuable though bacterial resistance will develop and remissions are often followed by recurrences and progress of the disease.

In addition to rest, reassurance, parasympatholytic or antispasmodic drugs, and use of chemotherapy and antibiotics, it is important that patients with ulcerative colitis have their nutrition maintained if possible. Machella (94) emphasizes combined use of a hydrolyzate and dextri-maltose solution and "medical ileostomy" accomplished by intubation of the small intestine and suction as a means of therapy during acute exacerbations He describes satisfactory remissions occurring in 13 patients.

Since ulcerative colitis is a disease caused by several etiologic factors and usually progresses to the formation of scar tissue and the development of structural damage to the colon with associated malnutrition, pain, obstruction, and hemorrhage, it seems probable that rehabilitation of the patient can best be accomplished by early surgical intervention. Ileostomy, if performed early, will avoid for many the need of subsequent partial or complete colectomy. Ileostomy can be accomplished employing the skin grafted appendage technique of Dragstedt *et al* (95) to avoid excoriation of the skin. If the flush ileostomy technique has been used, several new types of plastic bags are available. As emphasized by McKittrick & Moore (96), the diseased colon seldom heals sufficiently to allow subsequent closure of the ileostomy. Since patients are often referred for surgery as a last resort, the occurrence of perforation or hemorrhage and the need for subsequent colon resection still remains too high. The mortality risk at this stage of the disease is unfortunately great. Also, the occurrence of malignancy in these patients is not infrequent.

Diverticulitis—Diverticula of the colon may be multiple through its length or may be localized. They most often occur in the lower sigmoid Usually, patients can be managed by using a laxative diet and avoiding ingestion of fine particles such as seeds Chronic discomfort has, in the reviewers' experience, been relieved in a few patients by use of Banthine. Boyden (97) and Morhaus (98) have reviewed the surgical aspects of treatment for patients developing obstruction Temporary colostomy is occasionally used, or resection with primary anastomosis to restore continuity may sometimes be employed. Complications of diverticulitis include perforation and peritonitis, abscess formation, and occurrence of obstruction or fistulae At times, it is difficult to distinguish between carcinoma and diverticulitis, though usually carcinoma produces bleeding and diverticulitis does not but evidences greater inflammatory reaction.

Amebiasis—DeBakey & Ochsner (99) estimate that 10 per cent of the

LIVER AND BILIARY TRACT

Conventional tests of liver function frequently give variable results, and diagnosis of hepatic disease or dysfunction ordinarily requires use of several of these tests, careful evaluation of history and other findings, and occasionally, use of biopsy of the liver by aspiration or during surgical exploration. Cholecystograms are often useful in diagnosis of gall bladder disease but are of little value in patients with jaundice. Failure of visualization of the gall bladder gives indirect evidence of disease providing the dye can be absorbed from the intestine and is transported through the liver into the bile. The gall bladder, if properly functioning, can concentrate the bile.

Hepatitis.—Steele (114) has reviewed the records of 26 consecutive cases of homologous serum hepatitis and has compared the associated mortality rate of 34 per cent with that of 4 8 per cent in 63 cases of acute infectious (epidemic) hepatitis. He and other authors emphasize that homologous serum hepatitis following transfusion is an exceedingly serious problem. He recommends nitrogen mustard sterilization of blood and plasma as a relatively inexpensive and effective method for prevention of this disease. Kunkel & Labby (115) report the development of severe cirrhosis in five patients, two to six years after an attack of infectious hepatitis. The reviewers' observations agree with those of others that hepatitis may be followed by cirrhosis, this sequel appeared in one patient seven years following the jaundice and was confirmed by biopsy and a pathological diagnosis of Laennec's cirrhosis

Cirrhosis.—Ricketts, Kirsner, & Palmer (116), Douglass & Snell (117), and others have reviewed the medical aspects of portal cirrhosis. Many patients respond well to medical management. Gastrointestinal hemorrhage, particularly from bleeding varices of the lower esophagus and stomach, constitutes a major hazard and cause of death. This was the most frequent cause of death in the group reported by Douglass & Snell, with hepatic coma second. Sengstaken & Blakemore (118) have developed a useful method for balloon tamponage to control hemorrhage from esophageal varices Ascites requiring parecentesis and the administration of diuretic agents is also an important cause of disability. Depletion requires constant attention to replacement of fluids and proteins The treatment of patients with cirrhosis must be individualized since the course of development may be slow or rapid and the relative significance of varices with hemorrhage, ascites, or hepatic failure varies from patient to patient. Not infrequently, surgical intervention is necessary.

Splenectomy and omentopexy, by reducing the flow of arterial blood into the portal circulation and attempting diversion of venous outflow through new collaterals, is an old method of treatment which aided certain patients and, though currently not popular, may still remain a good initial treatment for some. A direct approach developed by Phemister & Humphreys (119) for treatment of recurring hemorrhages from esophageal and upper gastric varices is resection of the lower esophagus and the upper stomach with esophagogastrostomy. This seems indicated in those patients who have re-

there is a high incidence of malignant degeneration, particularly in those with a broad base. Fifty per cent of these polyps can be reached through a proctoscope, while those located higher in the colon require some form of colectomy. Familial polyposis is generally considered an indication for colectomy and ileosigmoidostomy. Subsequently, fulguration or avulsion through a proctoscope is used to remove polyps located in the remaining lower sigmoid colon and rectum. Incidence of malignant degeneration in familial polyposis is high.

Miscellaneous Diseases or Disorders of the Colon and Rectum

Megacolon.—Megacolon or Hirschsprung's disease produces serious constipation or obstipation in children. Symptoms ordinarily develop immediately after birth. This condition differs from the acquired megacolon occurring in adults, which is associated with constipation, enlargement of the sigmoid colon, and occasionally volvulus. In children [Grimson *et al.* (110)], the pathology may be of three types: group I, having uniform enlargement of all of the colon and a dilated or easily dilatable rectum; group II, having uniform dilatation of the proximal colon terminating in the sigmoid region in a normal-sized, but evidently abnormally functioning, segment of the sigmoid colon and rectum; and group III, having enormous dilatation of the upper sigmoid and descending colon with or without some dilatation of the proximal segments and a normal or dilated lower sigmoid and rectum. Surgery, in the reviewers' experience, is indicated only for extreme obstipation and abdominal distention occurring in the patients with group II type of megacolon. Operation was colectomy and ileosigmoidostomy so that liquid content from the ileum could be evacuated through a short segment of lower sigmoid and the rectum. A follow-up study [Grimson *et al.* (111)] revealed that patients with enlargement of the colon and rectum and patients with enlargement of the sigmoid colon alone, whether the rectum was dilated or not, responded well to medical management and, after a few years of moderate trouble, were often able to evacuate regularly. Recent experience adding bethanechol (urethane of β-methylcholine chloride; Urecholine) to the medical program has further confirmed these observations and lessened difficulty for these patients. Swenson (112) has used a modification of the pull-through technique developed by Bacon (104); he resects the normal sized segment of the lower sigmoid colon and rectum and draws the dilated sigmoid down through the preserved sphincter to form a new anus. This operation might be indicated for patients of the group II described above, but it does not seem warranted for the large number of patients Swenson reports and particularly for those of group III, as they, in the reviewers' experience, respond satisfactorily to medical management supplemented by use of bethanechol.

Volvulus.—Volvulus of the cecum may produce intestinal obstruction and require emergency reduction. Dixon & Meyer (113) analyze their experiences with 12 patients and recommend a method of retroperitoneal fixation. Volvulus of the sigmoid colon usually occurs in adults and may be associated with constipation or acquired megacolon. Treatment is reduction, or occasionally resection, of the redundant bowel.

PANCREAS

Diseases of the pancreas are being diagnosed with increasing frequency and accuracy and are being treated with new drugs and new surgical procedures. Reports on the pancreas are numerous.

Acute pancreatitis.—Although the exact etiology of acute pancreatitis is not established, reflux of bile into the pancreatic duct with or without obstruction of the ampulla of Vater, as postulated by Opie (128), continues to be a likely explanation. Doubilet & Mulholland (129) demonstrated in human patients reflux into the pancreas of radio-opaque material injected through tubes in the common duct. They suggest that a common channel, spasm of the sphincter of Oddi, and concentration of bile are factors in acute pancreatitis. Obstruction of the pancreatic ducts by epithelial metaplasia as postulated by Rich & Duff (130) is also usually considered among the causes of pancreatitis. Lium & Maddock (131) obstructed the pancreatic ducts of cats and stimulated the pancreas in various ways, thus producing pancreatitis. Other explanations of the cause of pancreatitis have been advanced. Clinically, however, it is evident that attacks frequently follow excesses of eating or drinking and are not uncommonly associated with coexisting disease of the gall bladder. Morse & Achs (132) reviewed 154 cases of acute pancreatitis and found that 63 per cent evidenced biliary disease.

The most important commonly accepted aid in the diagnosis of acute pancreatitis is elevation of the serum amylase, which occurs during the first 48 hr Experiments by Howard *et al.* (133) indicate that following pancreatic injury, enzymes are released directly into the blood stream rather than into lymph channels.

Acute hemorrhagic or necrotizing pancreatitis is associated with severe shock and a high mortality rate, whereas the nonnecrotizing or edematous form of pancreatitis is usually followed by spontaneous recovery. In either condition, preference for medical management consisting of intravenous therapy for shock, continuous gastric suction, and use of antispasmotic drugs has alternated at times with preference for laparotomy and cholecystectomy or cholecystostomy with diversion of bile to the exterior. There has never been unanimity of opinion Rhoads *et al.* (134) emphasize the frequency of co-existing disease of the gall bladder and prefer operative therapy They have performed cholecystostomy and drainage of the pancreas with a mortality rate of 3.2 per cent. Morse & Achs (132) recommend cholecystectomy a week or ten days after subsidence of symptoms of pancreatitis. Gage (135) describes relief of pain and clinical improvement following splanchnic block with procaine in the acute attack. This conservative procedure had been popular among surgeons in France and South America and has become popular here Shingleton *et al.* (136) observed a subnormal resting volume and enzyme content of the external secretions of the pancreas in patients after vagotomy or after administration of Banthine and found no increase with injection of secretin Splanchnicectomy patients, however, had normal volume and enzyme output and an increase with secretin Accordingly, they instituted treatment of acute pancreatitis by parenteral administration of

peated hemorrhages and a slowly progressing form of cirrhosis without evidence of much ascites or of hepatic failure. It is the opinion of the reviewers that bleeding in these patients is in part related to peptic ulceration of the mucosa overlying the varices and that use of antacid therapy or of Banthine should be part of the nonoperative management program. Operations designed to divert ascitic fluid into veins or subcutaneous spaces have been of dubious value. Heroic measures toward reduction of portal hypertension by shunting of blood from the portal venous system into the inferior vena cava have been attempted for years with a formidable mortality risk. Blakemore & Lord (120), Whipple (121), Linton *et al.* (122), Learmonth & Macpherson (123), and others have gradually improved techniques and accomplished reduction of mortality rates to 50 per cent or less Good results have been achieved in many of the surviving patients, and the operation of portal-caval shunt may be considered for serious complications of cirrhosis, providing sufficient liver function remains to permit surgery of this magnitude

Cholecystitis.—The indications for removal of the chronically diseased gall bladder with stones are well standardized. Risk of cholecystectomy has decreased, and as early operation is more frequently employed, complications such as jaundice, pancreatitis, gangrene, hydrops, and empyema are less frequently encountered. There still remains difference of opinion with regard to treatment of the patient seen during the first day or two of an acute attack. Some prefer nonoperative management unless complications occur and advise cholecystectomy subsequently during a quiescent interval. Unfortunately, many patients, thus treated, then refuse surgery and return later with other attacks and eventually with complications. Glenn (124) pioneered in the practice of removing the gall bladder during the first day or two of an acute attack. With increasing experience, this practice is more and more frequently employed by surgeons, with a low mortality risk and with excellent results Dunphy & Ross (125) and many others have recently reported results justifying use of cholecystectomy as an emergency treatment during the first day or two of an attack Surgeons generally agree that this should be the usual practice, though individualization of problems is necessary, particularly in the presence of jaundice or if accurate diagnosis is not possible.

Some patients experience postcholecystectomy pain commonly referred to as biliary dyskinesia. Celiac gangionectomy [Grimson *et al* (126)] or splanchnicectomy [Bingham, Ingelfinger & Smithwick (127)] relieves symptoms by interrupting pain pathways from the abdomen Currently, it is the reviewers' experience that continuing use of Banthine is helpful for these patients and may minimize the need for surgery

The most frequent pathology encountered in the common bile duct is obstruction by stones Usually, these have passed from the gall bladder and contain calcium, cholesterol, and bile pigment Rarely, pigment stones may develop in the common bile duct in the absence of the gall bladder. Treatment by choledocholithotomy is standardized. Neoplasms of the bile ducts occur infrequently and are treated as described below for carcinoma of the head of the pancreas. Carcinoma of the gall bladder itself occurs infrequently and is rarely recognized as a primary lesion.

It is recognized that unanimity of opinion with regard to etiology, diagnosis, or treatment of many diseases of the gastrointestinal tract does not exist. Also, it is recognized that continuing studies by physiologists, pharmacologists, pathologists, gastroenterologists, and surgeons will effect changes of opinion concerning etiology and treatment. Nevertheless, it is hoped that this chapter has afforded some expression of current beliefs and practices.

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the anticholinergic drug, Banthine, and observed prompt relief of pain and clinical improvement. Ripstein & Thompson (137) observed a 72 per cent mortality in experimental pancreatitis in normal dogs and in dogs previously treated by splanchnicectomy, but found that after vagotomy, the mortality rate was reduced to 24 per cent. These studies give support to the belief that acute pancreatitis should be treated conservatively, providing one individualizes problems and employs operation when the diagnosis is not certain or when co-existing disease of the gall bladder requires attention.

Chronic pancreatitis.—Chronic inflammation, fibrosis, and often calcification of the pancreas may lead to recurring episodes of pain and vomiting Pain and risk of addiction to drugs constitute the major clinical problems in this disease, since derangements of functions of the pancreas with diabetes, steatorrhea or obstruction of the common duct, and jaundice occur infrequently and only late. The older treatment by pancreatectomy has been largely abandoned. Interruption of pain pathways by celiac ganglionectomy [Grimson *et al* (126)] or splanchnicectomy [Bingham, Ingelfinger & Smithwick (127), Ray & Console (138) and others] is performed with little risk and has afforded gratifying relief. The celiac ganglionectomy is performed through a laparotomy incision which permits exploration of the abdomen and attention to any co-existing disease, whereas the splanchnicectomies are performed above the diaphragm without abdominal exploration. Doubilet & Mulholland (139) recommend exploration and section of the sphincter of Oddi. Although good results are recorded by these authors, poor results have been observed by others, and there is a definite question whether the divided sphincter will heal in such a fashion that obstruction is avoided Following the observation of Shingleton *et al.* (136), several patients with recurring pancreatitis have been followed with gratifying results on continuing use of Banthine and without surgery. For those requiring surgery, celiac ganglionectomy remains our preference

Carcinoma of the pancreas.—Although carcinomas of the body and tail of the pancreas are usually inoperable when recognized, carcinoma of the head of the pancreas usually produces symptoms and can be diagnosed early and often at a time when the tumor can be removed. Arkin & Weisberg (140), in a clinical and pathologic study, describe pain and rapid loss of weight as the commonest symptom of malignancy of the pancreas, and emphasize difficulty in diagnosis Exploration is indicated promptly in patients exhibiting the gradual development of painless jaundice, which often signifies carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater Whipple (141) and Brunschwig (142) were the pioneers in pancreaticoduodenectomy, and each abandoned their earlier two-stage operation, now preferring, when possible, the one-stage resection. Although Cattell (143), Allen & Welch (144), and others emphasize that the five-year survival rate is low, it nevertheless is evident that this operation is worthwhile and can be employed without great operative risk and with worthwhile palliation. The high mortality rate and poor prognosis following older procedures for relief of jaundice, cholecystogastrostomy, or cholecystoenterostomy have been emphasized by Dennis (145).

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DISEASES OF THE CARDIOVASCULAR SYSTEM[1]

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Methods of Diagnosis

The art of cardiac auscultation is given dynamic impetus by Levine (1), who emphasizes its specific value in the recognition of rheumatic heart disease and acute pericarditis and in the evaluation of heart block and tachycardia, and by Levine & Harvey (2) in their manual of clinical cardiac auscultation. Zinsser & Kay (3) note the value of straining, as in the Valsalva maneuver, in bringing out sounds and murmurs which are not heard at rest.

The ether (arm to lung) circulation time was tested in 84 per cent of 500 patients with congenital heart disease. A positive test was taken as pathognomonic of venous-arterial or mixed shunt. The prediction was verified in 27 patients at necropsy and in 75 by angiocardiography [Donzelot *et al.* (4)].

Simplification of electrocardiographic apparatus, particularly by direct recording, has spread the technique widely. Carter (5), in two special articles, reviews the value of the electrocardiogram in general practice, and Katz (6) its present status. New books on the topic are those of Evans (7) and of Wolff (8). The former includes a discussion of phonocardiography while the latter devotes the first part of his excellent book to basic principles. Of greater interest to the specialist is Goldberger's expert second edition of his manual (9) Special attention is given unipolar lead electrocardiography.

Myers (10) has developed schemata which elucidate the form of the normal precordial QRS complexes in the six Wilson leads and in left and right ventricular hypertrophy. Both from the theoretical and practical aspects, Hellerstein & Liebow's analysis (11) of the genesis of the T wave seems to us a fundamental contribution. Myers *et al.* (12, 13, 14) continue their correlations of electrocardiographic and pathologic changes in myocardial infarction

Master's two-step exercise test for latent coronary insufficiency (15) has been added to in the selection of standard exercises by age and sex. Coronary insufficiency is practically excluded if the standard and the double standard tests are negative False positives may result from excessive emotional tension [Master *et al.* (16)]. The simplicity of the Master test suggests that it will be widely adopted. However, tables of specific standard exercises do not mask the empiricism of a procedure which, when negative, should be repeated with doubled stimulus! The precipitating factors of angina pectoris are so complex that neither exercise nor anoxemia may uniformly elicit symptoms or the minimum diagnostic electrocardiographic changes.

[1] This review covers many but not all of the contributions published in the period from July, 1949 to July 1950. The abbreviation *et al.* is used reluctantly when more than three authors' names appear on a paper

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nique Starr *et al.* (33) describe their standardization of the ballistocardiogram by the simulation of cardiac function at necropsy and advocate it as a means of estimating cardiac strength. Nickerson *et al.* (34) find that the low-frequency, critically damped ballistocardiograph gives a diagnostic pattern (absence of the K-wave) in coarctation of the aorta. However, its field of widest usefulness may lie in the empirical detection of patterns which reflect latent myocardial inadequacy. Thus, the ballistocardiographic pattern is commonly abnormal in angina pectoris [Brown *et al.* (35)].

Kjellberg, Rudhe & Sjöstrand (36) find a correlation between total circulating hemoglobin, or blood volume, and heart volume, both at work and at rest Their analysis gives a simple explanation of the difference in pulse rate and heart volume of children and adults, men and women, and the athletically trained and untrained subjects More recently, Kjellberg and coworkers (37) have studied the nature of the correlation between height, pulse rate, and total hemoglobin and the effects on pulse of standing They conclude with McCann (38) that the pulmonary vascular bed functions as a blood depot whose content varies with total blood volume and whose function it is to regulate the filling of the left ventricle.

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Congenital Heart Disease

Dry *et al* (41) have handsomely assembled in book form their exhibit on congenital abnormalities of the heart and great vessels Since it represents the accumulation of their own experience, it is necessarily incomplete in minor respects, which do not derogate from its value In England, Campbell (42) has surveyed the relative significance of genetic and environmental factors in the genesis of cardiac anomalies, and Hollinger & Zak (43) have described techniques of cardiac catherization in diagnosis which Dexter (44) has summarized here.

The important advances depend upon the intimate co-operation with the surgeon of a clinical team of internists, clinical physiologists, and anesthesiologists Gross (45) has assembled a monograph on the surgery of these disorders and in 100 cases of coarctation of the aorta (46), finds that surgery relieved the hypertension completely in 71 and partially in nine. Of 11 fatalities in this series, seven would now be regarded as avoidable. With others, he describes a method for preservation and transplantation of frozen arterial grafts which increase the range of operability (47). Grafts interposed in the aorta or in shunts function as adequate bridges, but eventually consist only of intima and of fibrous tissue and, as such, might well in later years become foci of atherosclerotic deposition or of aneurysmal dilatation Wells, Rap-

The vectorcardiogram remains a field of more or less academic study of impulse dissociations and abnormalities [Conway, Cronvich & Burch (17)] Roentgenology continues to find new and wider fields of use. Habbe & Wright (18) report coronary arterial calcific plaques in 3 per cent of patients over 40 years of age and in half as many, calcification of heart valves. The importance of dilatation, often recognizable in postero-anterior roentgenograms and pulsation of the left subclavian artery as a sign of coarctation of the aorta, is emphasized by Stauffer & Rigler (19)

Steinberg *et al.* (20) performed angiocardiography in 60 patients with syphilitic aortitis, recording the angiocardiographic signs of this disease as aortic dilatation, irregularity of lumen, calcification of the ascending aorta, tortuosity, variations in thickness of the aortic wall, and aneurysm. They consider that uncomplicated arteriosclerosis does not dilate the aorta more than 38 mm. Peabody *et al.* (21) also emphasize the value of angiocardiography in the early anatomical diagnosis of aortic syphilis

Castellanos & Pereiras (22), who seem to be the first to have done retrograde aortography, review techniques Freeman and co-workers (23) successfully performed retrograde aortography by injection of 70 per cent iodopyracet (Diodrast) into the left common carotid in 13 of 15 patients suspected of coarctation of the aorta, and in nine of these, gave the exact location and degree of the stenosis In four patients, the aortograms contraindicated what would have been fruitless thoracotomy

The risk of angiography is indicated by Joyeux *et al.* (24), who gloomily report fatal gangrene following femoral arteriography. Dotter & Jackson (25) detail the results of a questionnaire on angiocardiography. Of 6,824 examinations reported, 26 resulted fatally The deaths occurred for the most part in patients with congenital heart disease, 17 of whom were cyanotic and five extremely ill. Three of the deaths were in mongols Angiographic techniques are not adapted to desultory or infrequent use

Electrokymography has only after the lapse of years begun to find clinical application Lewis & Terry (26) doubt that it will become a routine procedure. Gillick & Reynolds (27) describe a plateau-like pattern of the diastolic portion of the ventricular electrokymogram in patients with constrictive pericarditis which may be simulated in brachycardia and in extrapericardial conditions Brady & Taubman (28) found a movement of the ventricular border toward the auricle in diastolic gallop This movement coincided with the anomalous sound In gallop, there may be diastolic churning of the ventricular blood which by reflux closes the mitral valve Samet and co-workers (29) found that in heart block, delayed ventricular ejection and systolic accentuation (*bruit de cannon*) occurred when auricular and ventricular contractions fell close together [Sussman *et al* (30)] Dack *et al.* (31) have found ventricular electrokymography superior to roentgenograms in the recognition of areas of myocardial infarction

Introduction of new and simpler ballistocardiographs, such as those outlined by Dock & Taubman (32), is leading towards a wider use of this tech-

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paport & Sprague (48) direct attention to murmurs heard over the dorsal spine in coarctation and precordium, both diastolic and systolic, but more commonly the latter. The dorsal vibrations were especially definite in phonocardiograms. Goldman & Schroeder (49) have combined plethysmography and measurements of arterial pressure. The degree of coarctation is important since people with slight obstructions may live out their normal spans.

Zimmerman *et al.* (50) report successful catheterization of the left heart, but the risks are such that this will not be widely used. Taylor *et al.* (51) estimate in patent ductus arteriosus that flow through the shunt averaged some 40 per cent of cardiac output. Closure sharply decreases pulmonary arterial pressure and increases systemic systolic and diastolic pressures Preoperatively, patients with the tetralogy of Fallot show reticulocytosis and increased urobilin excretion. The rate of erythropoiesis is increased, and the red cells formed have abnormally short life spans. Reticulocyte count begins to decrease immediately after operation, while urobilin excretion is greatly increased for about a week. Thus, the major postoperative hematologic mechanism is increased destruction of red blood cells, analogous to that which occurs in the newborn [Josephs (52)].

Cardiac Irregularities

What seems by all odds a most dramatic contribution is the cinematic demonstration by Prinzmetal and co-workers (53) that auricular flutter arises from a single ectopic focus and not from Lewis' classical circus wave They would view the auricular irregularities as having a common mechanism. Concepts of the action of such drugs as quinidine will have to be modified in detail. In this connection, Nathanson *et al.* (54) find that methacholine (Mecholyl) acts systemically when applied intranasally in doses of 25 to 50 mg. They suggest that topical administration may be of limited value in patients who suffer from frequently recurrent and otherwise uncontrolled auricular tachycardias

The clinical effects of inorganic cations on cardiac arrhythmias have [illegible]

and may be useful in toxic rhythms caused by overdigitalization. It may be that potassium treats the patterns and not the patients! Malinow *et al* (56) have investigated electrocardiographic responses to oral dosages of 10 to 20 mg. of potassium chloride in patients with normal and abnormal rhythms. The consistent changes in the T waves they attribute to accelerated epicardial repolarization.

Ernstene & Proudfit (57) differentiate the electrocardiographic patterns of hypopotassemia and hypocalcemia. In contrast to the more complex patterns of hypopotassemia to which Bellet *et al.* (58) have also drawn attention, the hypocalcemic change is seen as a simple prolongation of Q-T interval without notable abnormality of T waves or addition of U waves

The electrocardiogram is a specially handy means of rapid diagnosis in hypopotassemia.

In a review of antifibrillatory drugs, DiPalma & Schultz (59) state their belief that quinidine is still the drug of choice in treatment and procaine the best tested agent in thoracic surgery. They note the probable usefulness of diaminoethanol derivatives in ventricular fibrillation and comment on the rapid advances being made in this field. In other studies, DiPalma *et al.* (60, 61) have investigated the antifibrillatory effect of drugs related to α-fagarine and describe the properties of one such drug which is effective in auricular fibrillation but initiates ventricular ectopic foci, which may go on to ventricular fibrillation. Gold (62) has compiled his wide experience with quinidine into a manual which details indications for its use in disorders of the heart. His emphasis is on the selection of cases and, in each case, the selection of a suitable dosage

Smithwick and co-workers (63) have studied the sympathetic cardiac innervation in patients who had nerve resections of varying degree. In sum, the observations indicate that cardiac acceleration is a co-ordinate function of sympathetic acceleration fibres which flow from the second to fifth thoracic segments (predominantly from the right side) and of vagal tone. Bilateral sympathetic resection causes the greatest decrease in resting and exercise pulse rates Denervation is conceded to be of benefit in hypertensive patients who show unusual degrees of tachycardia and in patients with disabling exertional or emotional tachycardia It may have value in a few patients with paroxysmal auricular tachycardia

Hanson & Rutledge (64) describe auricular fibrillation in patients with seemingly normal hearts. The arrhythmia in this form demands treatment for complications only. Armbrust & Levine (65) review 107 cases of paroxysmal ventricular tachycardia. The arrhythmia as such is relatively benign and can be controlled with quinidine. The onset of the attacks may be dramatically disabling.

Stevenson *et al* (66) describe certain common personality features of a small group of patients with normal hearts or organic disease who showed auricular irregularities. Their personalities were unduly subject to sustained anxiety, conflict, and depression.

Drugs

Untoward cardiovascular effects of drugs, some of them not used primarily for their vascular action, include tachycardia, hypotension, and electrocardiographic change during the acetaldehydemia incident to treatment with tetraethylthiuram disulfide (Antabus) [Raby & Lauritzen (67)] They direct attention to the dangers of this treatment in heart disease. Three fatalities, including two sudden deaths and two instances of prolonged myocardial ischemia, one of which proved fatal, followed the use of pitressin during cholecystography An electrocardiographic survey of 100 patients during this procedure shows little abnormality. Fatalities then seem to be

attributable to a special susceptibility (68). Since they have become essential in cardiac therapy, Vogl's charmingly told story of the discovery of the organic mercurial diuretics (69) is of special interest. It is another instance of Cannon's "serendipity"! Hermann's extensive studies of the new subcutaneously injectable mercurial mercaptomerin (Thiomerin) has been confirmed by Stewart *et al.* (70) and Grossman *et al.* (71) But the risk of hyponatremia *seems to contraindicate self-medication without careful supervision.* In this connection, Schneirson & Bergman (72) report five cases of acute urinary retention precipitated by mercurial diuresis.

Concentration-time curves of intravenously administered mercurial [meralluride (Mercuhydrin)] tagged with radiomercury [Threefoot *et al.* (73)] demonstrate that rapid urinary excretion accounts for most of the disappearance of radiomercury from the plasma. When the mercurial is given orally in enteric-coated tablets [Overman *et al.* (74)], the slower rate of urinary excretion suggests that the drug is poorly absorbed From this it follows that oral administration may well be ineffective or unpredictable. This prediction is not out of line with the experience of Shaffer *et al.* (75) who found that 5 of 50 patients responded well to parenteral mercurial and not to the oral drug. Duggan & Pitts (76) develop evidence for their view that the mercurial diuretics act by suppressing distal tubular reabsorption of sodium or chloride. Functional and histopathological considerations had heretofore led to a general acceptance of a primary action on proximal tubule. They also find an attractive explanation for the failure of mercurial diuresis in conditions in which glomerular filtration of sodium is depressed out of proportion to residual tubular mass Pitts & Sartorius (77) have comprehensively reviewed the whole field of diuretics in a survey which should *be read by any who are called upon to increase urine flow. It would* be useless to detail their considerations. One general rule is clearly stated: "One should employ the most benign drug capable of causing the desired fluid loss, in the minimum effective dose and at such intervals as are necessary to avoid marked fluctuations in weight" They view the future of diuretic therapy with real hope as better procedures are developed.

No less than 4 factors are now recognized as being casually related to overabsorption of water and salt by the renal venous pressure, namely, reduced glomerular filtration rate, elevated renal venous pressure, and excessive stimulation by adrenal cortical and posterior pituitary antidiuretic hormones It is possible that effective means might be found to raise filtration rate, reduce venous pressure, and inhibit either the secretion or the renal target action of the above mentioned hormones Such therapy would constitute a truly physiological means of combating edema.

With regard to digitalis generally, Burwell & Hendrix (78) consider the optimum dose as the minimum effective therapeutic dose and believe that the evidence points to an increasing narrowing of the margin between therapeutic and toxic dosages in heart disease In this connection, Dearing *et al.* (79) find that calculated therapeutic dosages of digitalis induced myocardial

lesions in two-thirds of 18 cats made hyperthyroid and in none of the 32 normals. Batterman & Gutner (80) describe 16 episodes in 15 patients in whom increasing congestive failure was the major manifestation of digitalis toxicity.

Ahmed *et al.* (81) have compared the effects of ouabain (G-Strophanthin) with digoxin in normal man and in congestive failure. Ouabain had no significant effect on cardiac output or venous filling pressure in normals. In heart failure, its primary effect was an increase in cardiac output with a secondary fall in venous pressure The net final effect of digoxin was similar but differed in timing and sequence. They conclude that ouabain must directly stimulate the myocardium, and they also modify their former view restricting the action of digoxin to a primary venous effect. In this connection, of considerable interest are [Ferrer, Harvey *et al.* (82, 83)] the contrasting responses of pulmonary arterial pressure to digoxin in right and left heart failure. In chronic cor pulmonale, digoxin increases cardiac output, decreases filling pressure, and increases pulmonary arterial pressure. Recovery from failure is associated with a later decrease in cardiac output and pulmonary pressure in most patients and improved aeration as indicated by an increase in oxygen saturation. In left failure, cardiac output and stroke volume are increased by digoxin while pulmonary arterial pressure decreases. In contrast to the normal state, relief of left failure by digoxin tends to decrease rather than increase peripheral resistance. The action of the drug is regarded as primarily myocardial.

Khellin has come into therapeutic use in angina pectoris. Rosenman *et al.* (84), like Dewar & Grimson (85), find considerable improvement in certain cases and failure in others, but recommend its trial. Simon *et al* (86) have re-evaluated papaverine in angina and consider it to be of little real value. Russek *et al.* (87) demonstrate that alcohol is ineffective as compared with nitroglycerin on the electrocardiographic response to standard exercise. Insofar as it suppresses pain, it may be dangerous Atkinson (88) evaluated the effect of tetraethylammonium in the treatment of angina pectoris over long periods. His guarded impression was that the treatment was of value in breaking up some of the components of the anginal mechanism and was most gratifying in status anginosus and coronary insufficiency. Clinical trials of the long-acting ganglionic blocking drugs may be of more interest.

Cardiac Dynamics and Failure

The controversy on the mechanism of congestive failure is resolving into a sober synthesis in which the heart retains its primacy This and many other aspects of heart disease are expertly and exhaustively considered in Friedberg's new text (89) and, from the physiological aspect, in Altschule's book (90) Particularly felicitous is the phrasing of Huckabee *et al.* (91), who state, "The only hemodynamic disturbance constant to all types of heart failure is that the cardiac output is reduced relative to the inflow load," and demonstrate that hypervolemia may be either a cause or a result

of heart failure. They propose an inclusive classification. Bing *et al.* (92) contribute to the clinical physiology of heart failure by their direct demonstration that the failing heart is inefficient in oxygen utilization.

Selkurt *et al.* (93) found in dogs that with decreased tubular sodium load, there is indeed an increase in the fraction of sodium reabsorbed. However, an accumulating body of evidence indicates that increased tubular reabsorption of sodium is at least as important a cause of sodium retention in congestive failure as is a decrease in renal tubular sodium load. Maxwell *et al.* (94) have shown that increased renal venous pressure is not sufficient cause of the renal ischemia found in heart failure. Edelman *et al.* (95) found renal blood flow decreased by about 70 per cent and glomerular filtration rate by 50 per cent in patients with rheumatic heart disease and congestive failure. There was a definite increase in renal arteriovenous oxygen difference. VEM[2] was found in the renal venous blood in 10 of the 12 patients; it was present three times in trace concentrations in samples from 13 normal control subjects. Release of VEM is attributed to the decreased renal oxygen tension. The hepatic venous blood of 10 of 11 patients showed VDM[3] in increased concentrations and traces only in 3 of 14 control subjects. Peripheral blood contained a mixture of varying proportions of VEM and VDM. The participation of these substances in the genetic mechanism of congestive failure is still for inference and conjecture.

A comparative survey of pulmonary arterial pressure in various species by Rodbard *et al.* (96) has culminated in a reasoned explanation. It is low in the higher vertebrates because of (*a*) the size of the pulmonary vascular bed, (*b*) the absence of tissue support for the capillaries, and (*c*) their distensibility. Corollaries of the two latter points are the facts that any marked increase in pulmonary arterial pressure tends both to pool blood in the lungs and to disturb respiratory exchange. Development of an interventricular septum not only separated arterial from venous blood, but also provided conditions in which systemic arterial pressure can vary independently of pulmonary pressure.

McCann (38) analyzes the respiratory regulation of circulation, taking the view that the lungs function as check-valves between the ventricles. He suggests that pulmonary vasoconstriction and associated bronchoconstriction can explain not only such an obvious lung-heart disorder as "tussive epilepsy" but may also participate in heart failure and angina pectoris. Thus, the effect of aminophylline on cardiac output can be more readily explained from its unquestionable pulmonary effects than from an assumed direct action on the myocardium Seemingly, inadequacies in the application of Starling's law in the intact organism can be resolved by the consideration that the pulmonary bed is far from passive, and its activity enables a separate application of the law to each ventricle Nylin *et al* (97), from the im-

[2] Vasoexcitor material.

[3] Vasodepressor material.

mediate volume of distribution of radiophosphorus, estimate that a third of the blood volume is normally in the heart and lungs; but Ebert *et al.* (98), in a similar study using T1824, estimate the fraction of the blood volume in lung, left heart, aorta, and major systemic arteries as only 20 per cent This volume of blood, referred to as Q, was normal in patients with mitral stenosis, but much increased in left ventricular failure, and did not correlate with vital capacity. The inference is that left ventricular diastolic content contributes more to Q than alterations in pulmonary blood volume.

In dogs, Bloomer *et al.* (99) found that ligation of the left pulmonary artery led to a progressive rise in left bronchial arterial flow so that in a few months the output of the left ventricle greatly exceeded that of the right. This dissociation may explain the left ventricular strain sometimes found in pulmonary stenosis or severe bronchiectasis

Chronic pulmonary insufficiency has been classified on physiological grounds by Baldwin *et al* (100). In order of increasing severity, the classes are (*a*) those who compensate for ordinary needs, (*b*) those with resting arterial anoxia, (*c*) a group who cannot compensate at rest and who have arterial anoxia and increased carbon dioxide content, and (*d*) a class showing polycythemia and congestive heart failure Of interest is the correlation of polycythemia with right heart failure rather than with anoxia as such The high cardiac output found in cor pulmonale in failure is interpreted as a response of a relatively normal myocardium to the stimulus of hypervolemia. The electrocardiographic pattern of right ventricular hypertrophy was nearly always present when pulmonary arterial pressure exceeded 30 mg. Hg but also appeared in some with lower pressures [Johnson *et al.* (101)]

Intermittent positive pressure breathing enables a more uniform alveolar aeration and increased arterial oxygen content in patients with pulmonary fibrosis and emphysema [Motley *et al* (102)] But even oxygen is hazardous in patients who are chronically anoxemic since it sometimes precipitates serious mental disturbances and may cause death in coma [Comroe *et al* (103)] The nature of these untoward responses is not apparent, although Motley (104) emphasizes respiratory acidosis as a sequel of treatment with 100 per cent oxygen. He recommends a 30 per cent concentration whenever oxygen is to be given over long periods, and, for ambient breathing in coma, concentrations to 70 per cent under intermittent positive pressure, thereby aiming to avoid both acidosis and atelectasis The possibility of maintaining oxygenation in the absence of pulmonary function has been explored experimentally by Clark *et al.* (105) These studies together with those of Stokes & Gibbons (106) and of Kolff (107) are aimed at temporarily substituting for both pulmonary and cardiac functions The technical difficulties are very great.

Beck's daring cardiac revascularization by arterial anastomosis with the coronary sinus (108) has been studied in dogs by Johns *et al* (109) They find that "these experiments indicate that this benefit is not sufficiently adequate (sic) or dependable to warrant clinical application at the present

of heart failure. They propose an inclusive classification. Bing *et al.* (92) contribute to the clinical physiology of heart failure by their direct demonstration that the failing heart is inefficient in oxygen utilization.

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that as little as 1 cc. of air may be lethal when injected into the left auricle. They suggest arterial embolization as the probable mechanism of so-called pleural shock Such embolization is recognized from air in the retinal arterioles, and by Liebermeister's sign of patchy pallor in the tongue. The head down, left lateral-prone position may protect both the cerebral and coronary vessels and subsequent administration of oxygen dissipate the bubbles In venous embolism, ordinarily much less serious, the cause of death is often a right-ventricular air-lock, so that Stallworth, Martin & Postlethwait (126) recommended immediate syringe aspiration of the ventricle. Medico-legally, air embolism is hard to detect and harder to prove. Kulka (127) has described a device for demonstrating it at necropsy.

Functional Heart Disease

A notable contribution in this field is Wolff's paper on life stress and cardiovascular disorders (128). In it he formulates a mass of data which demonstrate the intensity, quality, and variety of cardiovascular responses to stressful situations These include changes in heart action, electrocardiogram and peripheral resistance, and changes in the renal circulation which sometimes far outlast the change in arterial pressure. In general, pressor and vasoconstrictor responses to upsetting interview were more intense and prolonged in patients with essential hypertension, which suggests mechanisms which may accelerate its course. Stevenson *et al.* (129) describe the mechanism by which anxiety impairs exercise tolerance as an exaggerated cardiac mobilization with increased output, stroke volume, and rate. The combination of anxiety and the need for effort may account for the susceptibility of the chronically anxious to structural heart disease. At the very least, this must be the basis of many bouts of congestive heart failure which neither diet nor digitalis can explain

Peripheral Circulation

Cerebral vessels —Kety (130), who with Schmidt and co-workers has explored human cerebral circulation and function, authoritatively reviews this topic With Wechsler & Kleiss (131), he has shown that intravenous dosage with aminophylline has the unexpected effect of causing cerebrovascular vasoconstriction On the other hand, bilateral stellate ganglion block causes no change in cerebral blood flow or oxygen consumption in either normotensive or hypertensive patients [Harmel *et al* (132)] The mechanism of the beneficial effects which continue to be attributed (133) to this procedure in acute cerebral thrombosis and embolism remain obscure.

In contrast to essential hypertension, neither cerebrovascular resistance nor coronary artery resistance [Bing *et al.* (92)] are increased in coarctation of the aorta. It follows that this condition is not hemodynamically akin to renal or essential hypertension. Increased cerebral blood flow and pressure may also explain the comparative frequency of cerebral hemorrhage in co-

time." They had difficulty keeping the shunts open for more than a few days. The arterialization achieved was superficial. However, just as cardiac catheterization seems more injurious in dogs than in human patients [Banfield (110), Ellis *et al.* (111)], so it may be that the tendency of dog blood to clot thwarted some of their efforts and that Beck himself, at any rate, is justified in continuing his careful clinical trials. Vineberg's myocardial implantation of a mammary artery (112) is experimentally successful but will hardly be attempted soon in human patients.

SHOCK AND COLLAPSE

The nature and treatment of oligemic shock have been reviewed by Page (113), who places emphasis on the sequential changes of vascular reactivity and, in treatment of terminal shock, on intra-arterial transfusion. Zweifach (114) deals with the genetic participation of the VEM-VDM mechanism and the sequence of functional change in the small blood vessels as a guide to treatment. Remington *et al.* (115) differentiate three phases of response to hemorrhage in the dog. The concepts of the mechanisms of oligemic shock expressed by these authors are much the same. The differences lie mainly in the measurements made and in etiologic attributions.

Participation of the sympathetic system in the vasoconstriction of experimental oligemic shock has been studied by Wiggers *et al.* (116) and by Remington *et al* (117, 118). Inhibition of sympathetic activity by injection of N, N-dibenzyl-β-chloroethylamine (Dibenamine) alters the course, in that animals maintain their functions and survive at lower levels of arterial pressure than normal animals, but are also more sensitive to blood loss. The relative participation of sympathetic nerves, epinephrine, and norepinephrine is not tested Beecher (119) has compiled in one volume 10 articles on the treatment of war wound shock. The principles stated apply to shock in general. Resuscitation and anesthesia receive special attention.

The use of blood and plasma transfusions is carefully surveyed by Strumia & McGraw (120) Sampson & Singer (121) advocate transfusion of blood or plasma in patients who demonstrate hypotension of less than 85 mm. Hg as a sequel to myocardial infarction To be of value, treatment should be instituted within four hours Holden *et al.* (122) have observed that patients whose myocardial reserve had been impaired by arteriosclerotic heart disease did not tolerate the load of unnecessary or excessive postoperative transfusions Studies of the effects of transfusion in normal dogs and in dogs with myocardial infarction confirmed the impression, thus, it would seem that intra-arterial transfusion, now more widely used [Jones *et al.* (123), Mazella (123a)], would be the logical procedure in postinfarction shock.

Extra-arterial bleeding with subsequent intra-arterial transfusion of the patient's own blood (induced oligemia) is advocated by Gardner & Hale (124) as an aid to hemostasis during operations With arterial transfusion of any kind, air embolism is a serious hazard. Durant *et al* (125) have shown

sisted in nearly all those affected. The area involved had in the main increased.

Thrombotic arterial occlusive disease of the legs is monographically reviewed by Edwards (150) in a brief text on its diagnosis and treatment. Wartman (151) directs attention to bleeding into the intima as a precipitating cause of arterial occlusion in the legs. As in coronary and other arteries, capillaries which pathologically ramify through a diseased intima may rupture and lead to occlusion. This mechanism seems to be associated, at least in the three cases observed, with generalized hypertensive vascular disease, which, however, in our experience is a very unusual complication. Boyd *et al.* (152) report on a clinical and arteriographic review of nearly 500 cases of intermittent claudication, and they emphasize the frequency with which primary thrombosis of the popliteal arteries is the cause of this syndrome in young persons.

Malinow *et al.* (153) describe paroxysms of hypertension in certain patients with intermittent claudication. These were observed during standard exercises, did not directly correlate with pain, and were only partly abolished by tetraethylammonium. Malinow and co-workers suggest that a generalized vasoconstriction is sometimes an accompaniment of intermittent claudication, but increased cardiac output in an arteriosclerotic person would in part explain their observation. Naide (154) suggests simple measures (shortening the stride, favoring the affected leg, slowing the pace) which will lessen the demand of the calf muscles for blood and thereby relieve the claudication patient of much of his disability.

Freeman *et al.* (155) point out that those who have recovered from the ischemic effects of occlusion of an artery in an extremity may still present rest-pain, paresthesias and numbness—the so-called ischemic neuritis. Sympathectomy is contraindicated, but excision of a section of the thrombosed artery gives immediate relief Since arterectomy is not followed by any significant increase in circulation, it seems that it must act by interrupting a reflex which originates at the area of thrombosis An analogy can probably be drawn between this condition and some of the postcoronary syndromes.

Arterial embolization is reviewed by Andrus (156) Early (12 hr.) embolectomy is indicated in patients who are good surgical risks, but adds little to conservative measures in the aged and severely arteriosclerotic He advocates sympathectomy in most instances and the use of anticoagulants at once except in patients who are to undergo surgery The effectiveness of regional heparinization by intra-arterial drip has been demonstrated following embolectomy or other arterial surgery (157). This avoids the risks of systemic heparinization, and it may even improve anticoagulant activity at the site of arterial injury or repair.

A large proportion (roughly 25 per cent) of seemingly complicated and recurrent varicose veins particularly in the younger age groups are attributed to arteriovenous varices by Pratt (158) Treatment is based on wide excision of tributary veins and of arterial channels. Bauer (159) describes diagnosis

arctation. In this connection, Frankel (134) drew attention to the frequency with which a history of migraine is obtained in patients with spontaneous subarachnoid bleeding and suggested that intracerebral vasodilation during attacks may, over the course of years, weaken vessel walls. Bean *et al* (135) described a syndrome of acute focal cerebral disease precipitated by circulatory insufficiency secondary to myocardial infarction, which is to the brain what acute coronary insufficiency is to the heart.

Beck *et al.* (136) *have reported preliminarily on their attempts at increasing* cerebral blood flow by establishment of a carotid-jugular fistula in mentally retarded children. The most apparent benefit post-operatively is a decrease in the number and severity of convulsive seizures. However, we are told by some neurologists that this may follow nonspecifically as a sequel to any extensive trauma or operation.

Arteries and veins.—New books on the management of vascular diseases are those of Samuels (137) and Pratt (138) The latter's surgical text is recommended for its broad coverage and excellent illustrations. Surgical vascular *physiopathology is reviewed by Schumacher (139) Blood-clotting is informingly discussed from several points of view in a report of a Macy Conference* (140) and, from a more specialized aspect by Seegers (141) Contributions to instrumental diagnosis are numerous. Goetz (142) demonstrates the significance of the cutaneous venous circulation in tests of skin temperature and blood flow Winsor and co-workers (143) have compared various plethysmographic methods in patients with occlusive arterial disease, and they emphasize the value of the postocclusion plethysmogram. Winsor (144) has also used the systolic arterial gradients from thigh to toe as a guide to the site of arterial occlusion.

Kerslake & Cooper (145) find that in the hands and legs, the later period of vasodilation in response to warming the trunk is 10 to 15 sec The latency is the same when cuffs around the thighs are inflated to 200 mm Hg. The vasodilation is therefore due to a reflex with complex central nervous connections. Brigden *et al.* (146) show that forearm blood flow, right auricular [illegible] in the erect posture. People who faint [illegible] nd the fore- [illegible] s and pregnancy and in *some patients with central nervous system syphilis.*

Friedell *et al.* (147) have further developed their experience with the use of intravenously injected radioactive isotopes in the study of peripheral vascular disease and demonstrate the effects of priscoline in their "circulation index." The test proposed by Kety (148) as a measure of regional circulation is the reverse of this principle since it involves the rate of clearance of Na^{24} [illegible] *ion of Raynaud's phenome-* [illegible] disease, surveys its occupa- [illegible] g tools, and describes a test by *cold*-immersion. After a lapse of two and a half years, the condition per-

evaluated in this country. The latter gives great promise, since in the experienced hands of Wright (170) it is found to act more rapidly than dicumarol in decreasing prothrombin time and also to have less prolonged effect when treatment is stopped. Another new anticoagulant, phenylindandione (170a), has given encouraging results in 53 patients studied by Blaustein *et al.* (171). Its properties resemble those of ethyl biscoumacetate.

In the field of minor vascular surgery, Orbach (172) finds injection of an anionic detergent foam in volumes which contain as little as 0.03 cc. of the sulfate ester gives satisfactory sclerosis in 9 of 10 varicosities treated without any untoward effects

Rheumatic Fever

Etiology—Murphy & Swift (173) strengthened the belief that multiple streptococcal infection may cause rheumatic disease Rabbits sicken within 3 to 20 months after 2 to 10 skin infections with Group A streptococci of different serological type. Microscopic examination of those that succumbed and those sacrificed while sickened, revealed focal alterations in the connective tissue of the adventitia, valves, mural endocardium, epicardium, and myocardium. Cardiac granulomata similar to those of rheumatic fever were noted Only a small proportion of the rabbits developed the secardiac lesions But similarly, only a small proportion of infected human beings develop rheumatic heart disease The experimental procedure of multiple, successive infections follows the pattern encountered in rheumatic fever Swift has presented a comprehensive survey of a lifetime work (174) on the etiology of rheumatic fever which deserves the most careful and thoughtful reading and cannot, with justice, be abstracted.

The search for specific laboratory methods for detection of rheumatic disease continues. The phase reaction (175), cephalin-cholesterol flocculation [Kissane *et al* (176, 176a)], plasma hexosamine levels (177), and heparin tolerance (178) all are abnormal in many acute rheumatic fever patients but are not specific and, as Fischel states (179), there is no test for allergy in rheumatic patients which is not abnormal in patients recovering from streptococcal infections or other diseases

The tissue response to group A strain heat-killed streptococci in the skin of normal and rheumatic subjects has been studied by Humphrey & Pagel (180). Normal patients show only moderate reactions which, in the rheumatics, are greatly increased. While group A strain gave the most intense reactions, the severity of the reaction could not be correlated with any antigenic components of the streptococci.

Hench, Kendall and colleagues have two comprehensive papers on effects of cortisone and adrenocorticotrophic hormone (ACTH) on rheumatic patients. In the first of these [Sprague *et al* (181)], most of the characteristics of Cushing's syndrome are shown to result from large doses of these substances. Significant hypertension was observed in only one patient who may have had antecedent renal disease

and treatment of the lower leg stasis syndrome. In deep vein incompetence, there results chronic edema, ulceration, and pain. Popliteal vein ligation blocks the pressure head; the venous return then has to pass through small channels into the muscle veins of the thigh. Sixty-four of 78 patients who had been followed for more than one year after ligation showed steady progress towards healing. Analogous to Bauer's popliteal vein ligation is Glasser's recommendation (160) of ligation of the femoral vein immediately distal to the profunda branch in patients in the postphlebitic state.

The treatment of advanced lymphedema has been surveyed by deTakats & Evoy (161). In summary, they emphasize the great desirability of early treatment in the acute stage by elevation, movement, elastic compression, and when there is associated ilio-femoral thrombophlebitis, heparin. The problem in the chronic stage can to some extent be met by systemic measures for relief of edema (low-sodium diet, etc.). In 28 patients whose condition had become disabling, good results were obtained from a modified Kondoleon operation in 17, but little was gained cosmetically.

Rosenfeld, Langohr, and their co-workers (162, 163) report respectively on the effect of therapeutic cold and warmth in frostbite and thermal burns as observed experimentally in dogs. Cold at 10° C. seemed to retard the abnormal lymph flow and to decrease lymph protein concentration and edema of the affected area. In burns, cold had similar effects, but it also retarded healing and sometimes increased tissue damage Cold is useful only in the temporary relief of pain from small burns But the snowball treatment of the frostbitten cheek finds its justification.

The sympatholytic drugs have current interest. Nickerson & Gump (164) have reviewed the pharmacology of those related to N,N-dibenzyl-β-chloroethylamine (Dibenamine). Hoobler *et al* (165) describe in detail the effects of tetraethylammonium on peripheral blood flow in normal subjects With a dose of 500 mg , the sympathetic ganglionic blockade is incomplete since the vasodilation is only about half that obtained by paravertebral block However, it is greater than with aminophyllin, papaverine, nicotinic acid, nitroglycerin, and body heating Burt & Graham (166) describe the effects of the analogous, but longer-acting, pentamethonium and hexamethonium iodides Wakim *et al.* (167) report the peripheral vasodilator effects of benzazoline (Priscoline). As with tetraethylammonium, the greatest vasodilation occurred in the toes and feet.

Sympatholysis is better achieved by paravertebral lumbar sympathetic block than by drugs. Indeed, Ruben (168) believes that his method of continuous lumbar epidural block is especially effective. O'Connor *et al* (169) have drawn attention to a patient under treatment with dicumarol who suffered fatal retroperitoneal hemorrhage following lumbar sympathetic block. Systemic drugs may be especially useful in patients concurrently under anticoagulant treatment.

Two new anticoagulants, Paritol, a heparin analogue, and ethyl biscoumacetate (Tromexan), a dicumarol-like compound have yet to be fully

made in 19 of these, 17 of whom were controls, and 2 treated. Maliner *et al.* (187a) have further studied the problem of oral penicillin prophylaxis.

Rubbo, Holmes & Stokes (188) confirmed the observation that small daily doses of sulfanilamide given continuously reduced the recurrence rate. There was an increase in the number of sulfanilamide resistant organisms isolated from the treated group Penicillin was used in cases of manifest infection. Prophylaxis should best be instituted when a quiescent state has been reached after a major episode, preferably after the first attack.

Vascular lesions —Costero (189) has again confirmed Breutsch's work on the importance of cerebral vascular lesions as a cause of death in rheumatic fever. The old problem of whether rheumatic heart disease has any influence in development of coronary arterial degeneration seems to have been settled in the negative by Gardner & White (190). An exception to this may be coronary arteriosclerosis in the young [Saphir & Gore (191)] Rheumatic heart disease as demonstrated at necropsy among patients with rheumatoid arthritis is far higher than in the general population (192). This does not correspond with bedside experience, possibly because of the immobilization imposed by arthritis

Treatment —In the past year, the five approaches to the management of patients with rheumatic fever have been (*a*) treatment of the infections associated with the disease with penicillin, (*b*) treatment with cortisone and ACTH, (*c*) commisurotomy, (*d*) establishment of venous shunts for advanced mitral stenosis, and (*e*) administration of ascorbic acid. The first two have already been reviewed.

Commisurotomy is a relatively new operation which is now being performed in a number of centers with some success. Glover, O'Neill & Bailey (193) have re-established a considerable degree of vascular function without the production of significant additional regurgitation in about 30 cases Murray (194) and Baker, Brock & Campbell (194a) have recently discussed the technical aspects of the operation

Bland & Sweet (195) have devised a new procedure, an extracardiac shunt from the left auricle into the sytemic venous bed by anastomosing the dorsal segment branch of the right inferior pulmonary vein to the azygos vein. In three cases of advanced mitral stenosis with postoperative followups of 4 to 12 months, the repeated bouts of acute pulmonary edema have been prevented. One other patient died 11 days postoperatively of recurrence of acute rheumatic fever

Administration of 1 gm. of ascorbic acid by mouth four times a day to seven patients with rheumatic fever seemed to indicate that this substance had strong antirheumatic activity. Massell *et al.* (196) suggested this clinical trial on the basis of Rinehart's concept (333) that vitamin C deficiency played a part in the genesis of rheumatic fever. Their results are preliminary, and the outcome of the experiment will be watched with interest Cortisone-vitamin C interrelationships are noted experimentally by Schaffenburg *et al.* (197).

Hench *et al.* (182) in the second article report on eight patients with acute rheumatic fever and six with severe disseminated lupus erythematosus. The acute manifestations of rheumatic fever were generally promptly abolished by cortisone or ACTH. No evidence of new or increased old rheumatic carditis was observed within the following 8 to 10 months. Ancillary measures to treatment with these hormones are described in some detail. Thorn *et al.* (182a) have continued their careful studies on the relationship of pituitary-adrenal function to rheumatic disease.

Massell *et al.* (183) treated with ACTH 10 patients with severe rheumatic fever, most of whom had active carditis. The minimal effective dose was found to be between 20 and 50 mg. daily. All but 1 of 10 patients improved remarkably. Over 4 to 10 weeks, the rheumatic process became quiescent in five and damped in the others. Polyarthritis and fever were controlled most rapidly. Systolic and diastolic murmurs regressed in three patients. The sodium-retaining action of ACTH may partly counter its beneficial effect in the presence of congestive failure. The untoward reactions were severe mental depression in one patient, rounding of the face, and headache.

Further experience has also been added by McEwen *et al.* (184). The "C" reactive protein and antistreptolysin O titer fell to normal. The effect on rheumatic carditis was less definite; two patients showed no immediate improvement in heart failure, but one improved. These published cases added to many unpublished lead us to the view that neither short nor long term results are fully evaluated Opinion seems to run the gamut from optimism to pessimism All agree that the rheumatic process is either slowed or stopped while treatment is continued Little that is new has been published on the more fundamental mesenchymal mechanism of cortisone and ACTH. Dorfman & Moses (185) show a drop in hyaluronidase inhibitor during ACTH administration in children with rheumatic fever.

It will be recalled that much interest was created in 1935 by Crooke when he demonstrated hyaline cytoplasmic changes in the basophile cells of the pituitary in patients with Cushing's syndrome. Golden, Bondy & Sheldon (186) now find that administration of ACTH to patients results in an increase in the total number of pituitary basophils, Crooke's hyaline cytoplasmic changes in these cells, and basophilic stippling of many chromophobes. They suggest that these changes reflect storage of endogenous ACTH. If this view is confirmed, some of the speculation on the role of the pituitary in hypertension will require reorientation.

Prevention and prevalence of rheumatic disease.—The significant observation in this field seems to be the large scale demonstration (187) that early treatment of exudative pharyngitis and tonsilitis with procaine penicillin G in doses of 300,000 units on admission and again in 72 hr , strikingly reduced the incidence of rheumatic disease In the entire group of 1,650, 27 patients developed symptoms suggestive of acute rheumatic fever within 10 to 25 days of the initial infection. A definite diagnosis of acute rheumatic fever was

recently appeared in a fourth edition. Another new general text is that of Ziegler (208). The reviewers' text on hypertension (209) has appeared in a second, revised edition

Frant & Groen (210) using conventional methods, emphasize as a result of study of 418 ambulant patients that death rate in men is higher than women, that chronic nephritis increases the difference, and that in women the hypertension of toxemia of pregnancy materially increases mortality. Arterial pressure has been measured in 100 infants from one month to one year by Sujoy & Raznovich (211) and found to average 59/30 mm. Hg at one month and 95/58 at one year.

A grouping of signs and symptoms suggestive of adrenal cortical dysfunction has been made by Schroeder, Davies & Clark (212). Sudden onset of obesity of the cerebral type in women, menstrual irregularities, abnormally low concentration of sodium and chloride in sweat, and good response of the blood pressure to low salt diets make up the syndrome. The syndrome of malignant hypertension has received further study by Murphy and his group (213) They direct attention to the unusual features, such as spontaneous remission, lack of eyeground changes, lack of proteinuria and hematuria. They recommend sympathectomy in early cases. Not much progress has been made in unravelling the complicated mosaic composing the causative factors of the hypertension in patients, though some further understanding has been achieved in animals.

Lead poisoning seems to have again been found wanting as a cause of hypertension (214). A rather startling paper (215) by associates of the late Professor Volhard suggests importance to the functional state of the carotid sinus Procaine block of both sinuses in normotensive persons causes a sharp brief rise in presssure and pulse rate In hypertensives, the pressure rise is greater and more prolonged The authors suggest this is due to a lack of counter-regulation of the remaining pressor-receptors in the hypertensives, which in turn results from a higher vascular threshold for impulses associated with impaired elasticity. This is, in essence, placing hyposensitivity of the pressor-receptive system on an anatomical basis

The chloroform soluble formaldehydogenic steroids of some hypertensives' urines are increased in quantity [Corcoran & Page (216)]. This finding is consistent with overfunctioning of the adrenal cortex, primary or secondary, with a failure to degrade these steroids in the body, or with some peculiarity of renal excretion. In a preliminary report on three patients, Genest *et al.* (217) find changes in several steroid fractions when the salt intake was varied from high to low. Perera (218) has presented an excellent review of the relationship of the adrenal cortex and hypertension. From a different point of view, the same problem receives an imaginative and searching analysis by Selye (219).

It is impossible at this time to determine how far Selye's experimental work on the relationship of hypertension and vascular disease produced by lyophilized anterior pituitary powder (LAP) and DOCA in uni-nephrecto-

Bacterial Endocarditis

Little advance has been made in the understanding of bacterial endocarditis. Work seems to center chiefly on the lesions which remain after the disease is presumably healed and the kind of antibiotic therapy which is most effective. Kaplan *et al.* (198) followed 18 patients with subacute bacterial endocarditis cured by penicillin. Progressive cardiac disability occurred in six with dynamically significant residual aortic insufficiency, and three succumbed to congestive failure. Twelve patients showed no progressive cardiac disability, and in none of these was there significant aortic insufficiency. Saphir, Katz & Gore (199) have attempted to correlate electrocardiographic tracings with myocardial damage In 76 cases, anatomic changes were present in all. Serial electrocardiographic records, although not specifically diagnostic, indicated an active myocardial disease. A useful reference list has been provided (200) of articles published from 1936 to 1948, inclusive, on subacute bacterial endocarditis of nonstreptococcal origin

Electrophoretic studies of plasma proteins by Donzelot & Kaufman (201) showed moderate increases in γ-globulin in endocarditis with positive cultures The proportion of γ-globulin is very high in cases with bad prognosis and falls slowly and progressively with improvement. In rheumatic endocarditis, both α- and γ-globulins are greatly increased and decrease as improvement occurs

There seems to be a movement away from the use of anticoagulants in conjunction with sulfonamide or antibiotic therapy. For example, Cohen (202) reports two patients with massive cerebral hemorrhage following heparin and sulfapyridine therapy. King *et al.* (203) have compared the method of massive, short-term therapy with penicillin and 4′-carboxyphenylmethane sulfonanilide (Carinamide) with the prolonged moderate dose method. With the former, treatment was completed within 10 days or less. But in spite of the successful maintenance of very high blood penicillin levels, the infection persisted in seven of eight patients. Four of the seven failures were subsequently cured by prolonged treatment with moderate doses

The importance of (*a*) adequate daily doses of penicillin depending on sensitivity of the organism (not less than 500,000 units if sensitive and one million if resistant) and (*b*) continuous therapy for at least four to six weeks initially and longer if relapses occur, is again pointed out by Orgain & Donegan (204). A dosage schedule based on bacterial resistance is described by Schlichter, MacLean & Milzer (205)

Arterial Hypertension

Studies in the field of hypertension continue to increase in number, and the quality seems to be maintained. Many aspects are discussed in a Macy Conference publication (206) on factors regulating blood pressure. Stroud's textbook of cardiovascular disease (207), which is of course all-inclusive, has

with cerebral vascular disease of normal and of abnormal mental status. Those with normal mental status had significantly lower flows, higher A-V oxygen differences, and higher cerebral vascular resistance than normal young persons. Those with abnormal mental status had still lower flows, cerebral oxygen and glucose utilizations, and higher cerebral vascular resistance than those with normal mental status. Thus, a beginning has been made in the analysis of the effect of vascular disease on cerebral metabolic functions.

McCall (231) finds cerebral blood flow normal in pregnancy and toxemia, but resistance significantly increased in eclampsia. The oxygen consumption of the brain was decreased in eclampsia but not impaired in nonconvulsive toxemias The hypertensive part of the syndrome was only an incidental part of the study. Shenkin *et al* (232) and Crumpton *et al.* (233) have studied the problem of position on cerebral blood flow in normal and hypertensive patients after sympathectomy. The postsympathectomy patients differed in respect to cerebral blood flow with tilt, showing a decrease with 20 degrees head up tilt, whereas a majority of normotensives showed an increase.

Another method of clear potential value in the evaluation of patients with vascular disease is microscopy of the conjunctival vessels. Lack (234) uses magnifications up to 200 times In hypertensives, he finds a hypertension pattern in the capillary bed consisting of extensive narrowing, elongation and looping, fixed angularities or tortuosities, thickening of the walls, and loss of normal distensibility. Ninety-nine of 100 patients showed this pattern, and its severity correlated directly with the rise in diastolic pressure. Arteriolar pathology was observed in 80 per cent of the hypertensives as well

Mechanism.—Goldman and co-workers (235) noted no consistent change in glomerular filtration rate, renal plasma flow or filtration fraction during or following transfusion of hypertensives with blood from other hypertensives and later with normotensive blood. The problem of pressor and vasoconstrictor substances continued as vexed as ever Shorr's VEM is still only a phenomenon (334). VDM has been identified as ferritin, but ferritin has been shown to have no specific ability to depress the pressor action of epinephrine (236). Its large injection does not facilitate the production of shock. Much more work is required before the role these phenomena play in vascular disease can be assessed.

The so-called Trueta or Oxford shunt as a basic mechanism of hypertension seems to have about lost its vogue. Shunting does not occur in hypertensives, and ischemia of the renal cortex is not a necessary prerequisite for the production of hypertension. Thus, the enthusiastic and premature acclaim of an unjustified functional interpretation of sound morphological data has, as is so often the case, not been substantiated by mature consideration

Concentrates from 21 of 23 hypertensives' blood, when injected into rats, produced prolonged pressor effects, according to Stock & Schroeder (237). In the majority of extracts of 22 normal persons, the pressor effects were absent. Just why it was present in the minority is not made clear.

mized, salt-treated rats, can be applied to human hypertension. DOCA and LAP hypertension seem to have distinct mechanisms, but common pathological manifestations [Masson *et al.* (220)]. Selye's broad concept is stated in his inclusive book on stress (221).

In one hypertensive patient given 200 mg. of cortisone for 30 days, Perera *et al.* (222) found a preliminary rise in blood pressure followed by a small decline which persisted for several weeks after treatment was discontinued. Many observers will question whether these changes in blood pressure can be considered significant. From limited experience, the reviewers do not think it is.

The effect of sodium intake on the action of ACTH was studied by Ransohoff *et al.* (223) in one patient with essential hypertension. On a low salt diet, tetraethylammonium chloride (TEAC) reduced blood pressure more than in the control period. Administration of 100 mg. daily of ACTH raised the TEAC floor above the control values, but blood pressure remained unchanged. The left ventricular strain pattern disappeared and the Q-T interval became shorter. The TEAC floor closely parallels the metabolic response to ACTH.

Merrill & Smith (224) observed that during the course of hemodialysis with the Kolff artificial kidney, both systolic and diastolic pressure rise. The pressor response is the result of increased peripheral resistance and frequently of increased cardiac output. In patients with prolonged severe hypotension, irresponsive to blood or plasma, arterial pressure was also raised by dialysis. Could this response be due to the liberation of a norepinephrine-like substance as noted in dogs when cross-transfused (225), or is it a change in blood and extracellular fluid volume or the dialysis out of a depressor material? Their experience does not correspond with that of Kolff (226)

The clinical observation that hypertension is uncommon in patients with liver disease has received further support by Raaschou (227) who found the frequency and degree of hypertension was substantially higher in the control group than in patients with subacute liver atrophy. Insulin tolerance tests performed by Mirsky *et al* (228) show no difference between normal and essential hypertensive patients as regards the rate of blood sugar decrease after injection of a standard dose of insulin. But the rate of restoration is significantly delayed in hypertensives.

Various vascular areas have been subjected to more careful analysis of the changes elicited by hypertension due chiefly to the introduction of better methods. Recent work by Kety (229) shows that the constricted cerebral vessels of essential hypertension can partially relax in response to a fall in blood pressure elicited by differential spinal sympathetic block. The capacity to relax is not complete, so that with severe reduction of pressure, cerebral blood flow decreased and evidences of cerebral anoxia occurred. The circulation of the brain is thus, in this respect, analogous to that found in the kidney by the reviewers (157).

Scheinberg (230) examined the cerebral blood flow of a group of patients

cardia, postural hypotension, and glycosuria as signs of diagnostic value It is now quite well recognized that sustained hypertension may be associated with a pheochromocytoma, and another example of a well studied case has been published [Smith, Logue & Beard (243)]. An excellent practical discussion of diagnosis and treatment of pheochromocytomas has recently been published by Cahill & Aranow (244).

Assay of norepinephrine and epinephrine in extracts of nerves and other extra-adrenal tissues by von Euler (335) has shown that the chief sympathomimetic activity is due to norepinephrine. Further, Bulbring & Burn (245) have demonstrated release of norepinephrine as well as epinephrine from the adrenal glands in amounts varying from 20 to 80 per cent of the total. Holton (246) found nearly twice as much norepinephrine as epinephrine in an acid extract of a pheochromocytoma

A much more extensive clinical study of the problem has recently been presented by Goldenberg & Aranow (247). Analysis of 10 tumors showed that the norepinephrine concentration ranged from 14 to 97 per cent of the total catechol content, epinephrine making up the remainder. The more norepinephrine they contain, the more the clinical picture mimics essential hypertension

Hypertension persisted after removal of the tumors in 7 of 12 patients for periods of from months to years. Benzodioxane tests became negative and basal metabolic rates normal. The persistent elevation of blood pressure is due to some secondary mechanism, perhaps set in action by the prolonged presence of norepinephrine and epinephrine in the circulation It was indistinguishable from essential hypertension, but disappeared in several patients after varying lengths of time.

Tests for pheochromocytoma —A wide variety of adrenolytic or sympatholytic drugs continue to be used for the detection of epinephrine and norepinephrine-producing tumors Calkins *et al* (248) found no fall in arterial pressure after injection of benzodioxane (933-F, 2-piperidinomethyl-1, 4-benzodioxane) into 120 hypertensives Depressor (positive) responses were found in a verified pheochromocytoma and in a patient with a neuroblastoma. Removal of the latter caused a gradual fall in blood pressure and a negative response to 933-F With recurrence, the pressure rose again and a positive response to 933-F reappeared. In contrast, Taliaferro, Adams & Haag (249) studied a patient with renal hypertension in whom benzodioxane caused a sharp fall in blood pressure, which, on repetition four times, resulted in no change in blood pressure. A depressor response after benzodioxane does not necessarily indicate the presence of pheochromocytoma, nor, according to Wilson (250), does it exclude it

Another interesting case of pheochromocytoma has been published by Shapiro *et al* (251) in which 933-F produced an immediate fall in pressure to normal. Benzodioxane also appears to block norepinephrine in human beings and hence can be used in patients with tumors which secrete largely norepinephrine [Goldenberg & Aranow (252)] Since they point towards a re-

Schroeder & Olsen (238) have recently entitled the substance contained in those extracts, "Pherentasin," and further defined it as a water, alcohol, and chloroform soluble substance recoverable in concentrations of 10 to 20 μg per l of blood It is *somewhat unstable, nonprotein, and amine-like. It is concluded* that this active pressor substance appears in the blood of most types of hypertension, increases in amount as nephrosclerosis develops, often disappears in the malignant stage, and does not usually accompany one specially defined hypertensive syndrome. Uncertain as the results currently are, it is this sort of investigation which is so necessary to progress in understanding of the mechanism of hypertension

Further work on the chemical constitution of serotonin, the serum vasoconstrictor, has been presented by Rapport (239). Serotonin as crystallized from blood is a complex of equimolecular parts of creatinine and the sulfuric acid salt of serotonin. Elementary analysis of the crystalline picrate of serotonin confirmed the empirical formula $C_{10}H_{14}O_2N_2$ obtained by deducting creatinine from the complex isolated from serum. Tentatively, serotonin was assigned the structure of 5-hydroxy-tryptamine, containing water of crystallization.

Mechanism of Cushing's syndrome and toxemia of pregnancy—Heinbecker has reviewed again his concept of the mechanism of Cushing's syndrome and added more evidence to support it (240). He conceived of Cushing's syndrome as having three primary causes, a tumor of the adrenal cortex, atrophy of the paired paraventricular hypothalamic nuclei, or a tumor of the ovary secreting progesterone These primary causes result in endocrine imbalance characterized by overaction of the hypophyseal eosinophile cells and underaction of the basophile cells. Later, because of atrophic changes in the thyroid gland and gonads, the basophile cells may increase above normal numbers. But these cells are hyalinized and functionally depressed. The increased action of the eosinophiles leads to augmentation of the function of those structures to which the eosinophiles are trophic, namely, adrenal cortex, corpora lutea, androgenic cells, and renal tubular cells. *Depression of* hypophyseal basophilic cells results in depression of the thyroid gland and failure of maturation of the ova and seminiferous cells The hypertension is regarded as a response to the overactivity of the hypophyseal eosinophile-adrenal-renin-angiotonin complex It is an interesting concept which will require much careful work to prove or disprove Findley (241) has reviewed the evidence in its favor

Pheochromocytoma—By far the most important advance in our knowledge of pheochromocytoma is the finding by various investigators that they contain norepinephrine as well as epinephrine. Many single case reports have appeared and much interest has been shown in tests for the presence of tumor by agents that block the action of epinephrine and/or norepinephrine. Smithwick *et al* (242) call attention to the importance of excessive perspiration, vasomotor phenomena, normal cold pressor response, periodic elevations of temperature, blood sugar and basal metabolic rate, postural tachy-

the results not be clouded by inadequate studies. Yet this continues to be the rule rather than the exception. An example is the use of irradiation of the pituitary gland as a treatment for hypertensive vasculăr disease. From time to time this method has been highly recommended by able clinicians. Yet now, Best *et al.* (263) report it to be useless. Wolff (264) continues his thorough study of life stresses on cardiovascular disease. This is one of the few such being conducted There is no indication as yet that a sympatholytic agent has been found to be of value in the treatment of hypertensive patients, though several new ones have been tested [Grimson *et al.* (265), Nickerson (266)].

Dietary management of hypertension is gradually being clarified as the rather excessive emotional reactions to the subject seem now to be cooling. Chapman & Gibbons (267) have recently reviewed the matter in detail and have done it well. Results of study of 39 patients with essential hypertension during the 10 months siege of Budapest when the diet was free of animal protein showed no change in blood pressure after this long period of deprivation [Kohări & Kuchări (268)].

Some success is reported from various clinics on the use of low, and drastically low, salt diets [Bang, Bechgaard & Nielsen (269), Landowne, Thompson & Ruby (270)] The results vary widely due to differences in the way the various groups were studied and possibly in no small measure to the way the patients adhered to the diets. It is almost a rule that most outpatients are not actually on a drastic low-salt diet, and it is difficult enough to keep the intake at 200 mg. when the patient is in the hospital A cation exchange resin can restrict the absorption of sodium from the intestine as originally suggested by Dock (336), but is not a full answer to the problem of sodium restriction. Berger *et al* (271) report some success with an exchange resin which fixed some sodium and induced a compensated acidosis by liberation of hydrogen ions in exchange for sodium ions Further work on the renal capacity of hypertensives to excrete sodium has been presented [Gregory *et al* (272)] The syndrome of salt depletion is well described by Soloff & Zatuchni (273) and by Schroeder (274). The effect of change in salt content of the diet on the effects of ACTH in essential hypertension was noted above [Ransohoff *et al.* (275)].

Rice diet—A very good summary of the results of the rice diet has recently appeared from Kempner's pen (276) in which he makes a strong plea for its continued use. He does not accept the view that the chief virtue of the diet lies in its being low in salt and calories The reviewers' own results, however, offer proof that in some patients, at least, this is so (277) since when salt was added to the rice diet, blood pressure rose, and its withdrawal again elicited a fall in pressure. Disagreement continues on whether patients on the diet can maintain nitrogen equilibrium. Peschel & Peschel (278) find five slightly negative and seven slightly positive Two in our experience seemed to be in balance Renal functional studies by Weston *et al* (279) and

duction of the risk of operation, the observations of Grimson *et al.* (253) and of Bartels & Cattell (254) on the operative use of adrenolytic drugs are of special interest.

Green (255) reports on a patient with paroxysmal hypertension who within 6 min. of receiving benzodioxane exhibited a rise of 20/14 mm. Hg associated with convulsive twitchings, thick speech and other signs mimicking her previous attacks. Benzodioxane may be dangerously pressor in susceptible persons. These varied reports demonstrate the commonly overlooked fact that this group of drugs have highly complex actions and that, while in many cases simple rules may be followed in their use, in others gross error may result. Benzodioxane does not block the cold pressor test [Berris & Aagaard (256)] which accords with the concept of a neurogenic mechanism of this response.

Other blocking agents.—Ferris and his associates (257) have continued their studies on the effect of TEAC and veratrum viride on the blood pressure in normal and toxemic pregnancy. The blood pressure of the toxemic hypertensive consistently falls when veratrum is given. In normal pregnancy, TEAC produces a fall, while veratrum yields negligible responses In toxemia, TEAC produces only minimal falls while veratrum yields marked lowering. Frew & Rosenheim (258) have studied the effect of tetraethylammonium bromide (TEAB) and secobarbital (Seconal) on the assumption that both drugs act upon the neurogenic element of the hypertension but at different levels of the reflex arc No difference was detected in the response of patients with essential hypertension and hypertension secondary to chronic renal disease. Again, it should be pointed out that almost none of these results can as yet be interpreted with any degree of finality. At least it is encouraging that TEAB does not produce a fall in cardiac index with fall in arterial pressure in either normotensive or hypertensive patients.

The extreme complexity of this action of these drugs and the complexity of the changing reactions of the body to them has been the subject of a series of papers by Page & Taylor (259) The results obtained in the laboratory illustrate the protean complexity of drug-body response interactions.

It is a pity to have to record that more and more evidence is accumulating against the significance of the cold pressor and possibly other similar tests The latest is a followup study for seven years on 166 officers by Armstrong & Rafferty (260). They found the test not correlated with measures of hypertensive tendency, age, flying time or "basal" blood pressure Incidentally, the number of hours a career pilot has flown was not found correlated with hypertensive tendencies, provided he had passed careful physical examinations annually. Postelli & Palmer (261) also were unable to classify patients into different grades or indicate prognosis by pressor-depressor tests.

Treatment.—Ayman (262) has again pointed out the even greater necessity today for critical evaluation of reports on therapy of hypertension. With the multiplicity of agents being suggested, it is the more urgent that

a fall in basal arterial pressure greater than 15/10 mm. Hg with thiocyanate compared with the previous lack of significant change from placebos. Two-thirds of Fischman's patients (289) exhibited a fall of 10 to 25 per cent in both systolic and diastolic pressure, but only one-third showed a comparable rise after withdrawal of the drug. Reversal of electrocardiographic abnormalities, such as follows sympathectomy, were not observed after thiocyanate. Moister & Freis (290) show that single doses of thiocyanate are excreted quantitatively in the urine, but after prolonged administration, the balance becomes positive, either from intracellular storage or destruction. The latter is the more likely possibility.

Dihydroergocornine.—In an excellent study of the hemodynamic effects of intravenously injected dehydroergocornine (DHO 180) Freis *et al.* (291) show that vasopressor responses to a variety of procedures were inhibited or abolished. Blood flow through the forearm, leg, and hepatic-portal circuit varied irregularly. Renal blood flow, glomerular filtration rate, and urine flow decreased initially with the fall in arterial pressure but later returned to the control levels, although oliguria persisted, because of increased tubular reabsorption of water. The fall in arterial pressure was accompanied by no change in cardiac output, hence total peripheral resistance was reduced. The fall in blood pressure from intramuscular injection causes no change in cerebral blood flow or cerebral arteriovenous oxygen difference so that cerebral vascular resistance must also be decreased [Hafkenschiel *et al.* (292)].

Bello, Moss & Weiss (293) and Tandowsky (294) found the drug to be transiently depressor when administered intravenously but inactive by mouth. While they retain theoretical interest, the dihydrogenated ergot alkaloids so far studied have not proved to be of value in the treatment of hypertension. This opinion is at variance with that of Kappert (295) who finds that a mixture of three dihydroergot derivatives, i.e., dihydroergocristine, dihydroergokryptine, and dihydroergocornine (Hydergine; CCK 179), is superior to bromides, barbiturates, and purine derivatives, which says but little. He lists a variety of objectively measurable improvements which indicate that the drug has value, but investigators in this country are not convinced.

Rauwolfia serpentina.—Tablets of the dried root are said by Vakil (296) to give moderate reduction in blood pressure. The data do not show adequate control periods.

Veratrum.—Interest in this very old drug has been awakened largely because chemists have separated and purified many of the alkaloids of the complex mixture extracted from the plants. The irregularity of the action of the galenic preparations and their nauseant property all but discredited them as therapeutic agents. A few pure compounds are now available in minute amounts for study, and these have in large part been used for the beautiful pharmacological studies of Krayer (297) to whose monograph the reader is referred. Mailman & Krayer (298) have recently reported on the acute effects of intravenous protoveratrine and veratridine. Both drugs pro-

Currens *et al.* (279a) for short periods on low-sodium and rice diets show decrease in glomerular filtration. In a few patients on the rice diet, Tm_{PAH} decreased.

Sympathectomy.—The observations of Taquini & Vilamil (280) show that after thoracolumbar sympathectomy, blood volume greatly increases immediately after the operation and is even somewhat increased after a year or more, demonstrating the increased vascular capacity of the splanchnic area resulting from operation. It is interesting that this view reappears after 15 years of being completely discredited.

Precise anatomical and functional analysis of the spinal nerve roots in dogs demonstrate the persistence of accessory vasoconstrictor pathways following verified lumbar sympathectomy. Ganglionated cell aggregates were found in relation to ventral primary divisions of the second, third, fourth, and sixth lumbar nerves. The postganglionic fibers of these cells apparently pass directly along the ventral primary ramus of the spinal nerve without entering the paravertebral ganglionic chain. They would not be interrupted by lumbar ganglionectomy (281).

The knotty problem of whether sympathectomy prolongs life is answered affirmatively by Hammarstrom & Bechgaard (282) Grimson *et al.* (283) have made some interesting observations on their patients subjected to total sympathectomy. Postural lowering in blood pressure has persisted in all but a few of their patients It is not associated with tachycardia, since heart and adrenal glands were denervated The most serious complication, even several months after operation, is pain which occurs in all and is intense in many. Excessive sweating occurs in areas of regeneration or areas not denervated, and partial obstruction of the nose by swelling of the mucous membranes was very common Progress of the vascular diseases seems to have been retarded in the 113 patients operated upon. The only observations that have not indicated improvement are those based on heart size and electrocardiogram.

Keith, Woolf & Gilchrist (284) describe their results from 96 patients treated medically and 56 surgically (chiefly Smithwick technique) Those surgically treated had fewer symptoms after three years, but only slight differences in diastolic pressure The mortality rate in the two groups was about the same Platt & Stanbury (285) report that only 11 out of 80 patients exhibited a significant and lasting reduction in blood pressure when patients were operated upon in whom the prognosis was judged unfavorable, usually with resting diastolic pressures of 120 mm Hg. They generally condemn the operation, but believe there is a small group in which sympathectomy produces a lasting and significant benefit Padilla, Cossio & Berreta (286) find only 3 of 27 patients with favorable results The side effects and complications of sympathectomy have been ably described by Fowler & de Takats (287). Chemical sympathetic blockade in hypertension is discussed by Nickerson (287a).

Thiocyanate.—Alstad (288) finds 62 per cent of 32 hypertensives showed

fatty and fibrotic degeneration of the intima—has its initiation as medial calcification which foreshadows the formation of intimal plaques, has been further considered by Lansing, Alex & Rosenthal (306). They find a sharp increase in the calcium content of elastin from 25 to 50 years, along with a significant increase in aspartic acid. A shift in the composition of elastin with age probably accounts for the increased calcium content. Lansing believes that intimal plaques do not occur without calcification of the media or other medial change, such as syphilitic aortitis. His evidence justifies a re-examination of this whole problem from the morphologic viewpoint It is experimentally supported by Schlichter's studies (307) on aortic vascularization.

Molecular microdistillation of the esters of the intima of human aortas shows them to be similar in composition to those of serum [Koehler & Hill (308)]. This adds one more piece of evidence to our concept that the lipid mixture in the aorta was similar in composition to that of blood, both in rabbits fed cholesterol or human atherosclerosis.

Serum cholesterol levels.—It has become increasingly clear that the level of cholesterol in blood is not a reliable index of the presence of atherosclerosis, although when the level is high for long periods of time, the chance of development of atherosclerosis is greatly increased. A pressing problem is the relationship of normal or slightly elevated blood cholesterol values to coronary atherosclerosis The evidence from a variety of sources (309) seems to indicate instability of the serum cholesterol levels as a fairly regular accompaniment of coronary arterial thrombosis Older work has suggested that in any individual, the values are quite constant although they vary considerably from person to person But an unstable level of blood cholesterol is hardly a sound basis for following the development of atherosclerosis.

The effect of age on serum cholesterol levels continues to be studied [Kornerup (310)] Fifteen years ago, we found no increase in aged persons who were carefully selected for good physical status Keys *et al.* (311) now report that values are lowest in late adolescence, highest in the 50's and decrease in old age, the range being 174 to 267 mg Sperry & Webb (312) reexamined a number of subjects they had studied 13 to 15 years before, finding in over half of the men no appreciable change in either direction from the earlier level In the remaining men and all but one of the women, there was an increase from 10 to 30 per cent Thus, an increase with age is common but not obligatory Whether disease was present in any of these individuals is not stated. Therefore, as the problem stands, proof has yet to be offered that aging as such is associated with rising blood lipid values.

The problem of diet and blood cholesterol values is even more vexing Thus, Wilkinson, Blecha & Reimer (313) find no relation between the amount [illegible]

rapid fall in serum cholesterol, averaging 85 mg. per cent when patients sub-

duce a striking fall in blood pressure in both essential and renal hypertension with simultaneous fall in heart rate. Atropine blocks this without abolishing the vasodepressor effect. An inverted or flat T wave in lead 1 may revert to upright during the hypotensive period. A purified, biologically standardized mixture of veratrum alkaloids (Veriloid) is now for sale. Its pharmacology has in part been studied by Stutzman & Maison (299). In dogs, they find the hypotensive action unaltered by atropine, cervical vagotomy, and carotid sinus denervation. Wilkins, Stanton & Freis (300) have made a most extensive study of this drug, and their results show beyond doubt that in many patients it has real value. The reviewers' own experience of the past year confirms this By no means all patients respond to Veriloid, but when a response occurs, it is of sufficient magnitude to be beyond any chance variation of the blood pressure and appears to be of therapeutic value. Therapy is sometimes complicated by a narrowing of the toxic-therapeutic dose difference.

Pyrogen.—Further experience with various pyrogens for the treatment of patients with malignant hypertension has been reported by Taylor, Corcoran & Page (301). Eight of eleven patients showing reversal were alive without further treatment, an average survival time of 32 months. Empirically, it seems that patients are most likely to respond favorably when the Tm_{PAH} is above 33 mg. per min It has not as yet been determined which pyrogen is the most useful. Page & Taylor (302) have described the technique of treatment.

Arteriosclerosis

Much work on arteriosclerosis using experimental animals has appeared in the past year, most of which was presented before the young but important American Society for the Study of Arteriosclerosis. Far less has been done on human arteriosclerosis. Altschul's interesting *Selected Studies on Arteriosclerosis* has just appeared (337).

Faber (303) has studied the problem of the metachromatic tissue in blood vessels and has concluded that this staining reaction is closely identified with receptivity of the tissue for cholesterol. Presence of these carbohydrate-sulfuric acid esters is an index of increased tissue susceptibility, possibly attributable to the esters as such. Hypertension increases the dry weight, cholesterol, and calcium content of the aorta, but obesity does not [Faber & Lund (304)].

Analysis of normal aortas from birth to 35 years shows that the increase in cholesterol was confined chiefly to free cholesterol according to Buck & Rossiter (305). After 35 years, the increase is chiefly in the ester fraction. An increase in the concentration of sphingomyelin accounts for all the increase in phosphatide with age. When macroscopic evidence of atherosclerosis appeared, both free and ester cholesterol appeared as well as phosphatide and neutral fat.

The view that arteriosclerosis—defined as an age dependent process of

of cholesterol develop these molecules in their serum. They were always present in rabbit's serum when the total cholesterol was above 200 mg. per cent and in man when above 300 mg. per cent. (*d*) Less extensive data suggest their presence in nephrosis, apoplexy, and diabetes But the correlation between the occurrence of S_f 10 to 20 molecules and the plasma cholesterol has only been crudely established. A low cholesterol value does not assure its absence. A very important aspect of this work is Gofman's finding that low cholesterol diets lowers the concentration of the S_f 10 to 20 molecules. The implications are so obvious that it seems most important at the moment to warn against the drawing of premature conclusions.

Lipotropic agents.—A variety of conflicting data is appearing on the effects of lipotropic agents in experimental animals Currently, it is unwise to draw conclusions from this evidence as to the part they may play in atherosclerosis. The data from human beings is even less reliable The commercial exploitation of choline, inositol, and other such drugs as is being done has not the slightest justification, and these will join rutin as drugs sold for wide consumption on the basis of ignorance.

Arteriosclerosis of Various Vascular Beds

Coronary arteries —Coronary disease, presumably on the basis of hyperlipemia, continues to be described Alvord (321) has described a family of 30 with hereditary hyperlipemia in whom 18 had coronary disease. Families with xanthoma also exhibit a high incidence of hypercholesterolemia and coronary disease according to Adelsberg, Parets & Boas (322). Serum cholesterol was elevated above 300 mg per cent in 122 of the 175 patients.

Study of the relationship of coronary atherosclerosis and age (30 to 89 years) in male patients by White, Edwards & Dry (323) shows that the degree of sclerosis is not primarily related to age as is commonly assumed Nor do myocardial hypertrophy and coronary atherosclerosis parallel one another. Thus, more and more evidence accumulates showing that coronary atherosclerosis is a disease in its own right, and while it occurs in older age groups, it is not a necessary accompaniment of aging Prognosis has again been discussed [Billings *et al* (324)]

Corday *et al* (325) have shown that, in the presence of experimental myocardial infarction, hypotension spreads the zone of incontractile and cyanotic tissue, and they have reproduced in dogs the mechanism of the syndrome of acute myocardial insufficiency

Renal arteriosclerosis —Wilens & Elster (326) point out that lipid deposition in the walls of the renal arteries occurs as commonly as it does in the intima of large arteries It is somewhat more common in hypertensive or diabetic women than in similar groups of men. Renal arteriolar lipidosis is significantly increased in all forms of hypertension except that associated with glomerulonephritis Thus, lipid deposition may be an early and essential feature in the hyalinization and thickening of arterioles observed in hypertension

sisted on a fat-free diet which supplied 2,000 to 4,000 calories. The rice diet has a similar effect. Thus, to cause a decrease, a diet must be really fat-free and not merely fat-poor.

More evidence has been added to support the notion that serum lipid emulsions are stabilized by serum phosphatides. Thus, Ahrens & Kunkel (315) note that sera with high total lipids are clear when a large part is phosphatide, as occurs in obstructive jaundice. Bile salts may be another dispersing agent. Normally, increase in total plasma lipid is due especially to increase in neutral fat and phosphatide, cholesterol ester and free cholesterol increasing least. This is just the reverse of what Gertler & Garn (316) found in patients with coronary disease In them, the phosphatides do not keep pace with the rise in serum cholesterol. Zinn & Griffith (317) compared the ratio of large fat droplets (chylo-microns) to the total number (lipomicrons) in normals, arteriosclerotic diabetic patients, and patients with myocardial infarcts This evidence suggests a distinct increase in the larger particles.

Lipoprotein.—Evidence has accumulated that the steroids and other lipids are loosely bound to plasma protein With the growth of the idea that the lipids, especially cholesterol, are atherogenic, more and more effort is being put into study of lipoprotein, culminating in the announcement of Gofman and co-workers (318) that certain specific lipoprotein molecules are to be associated with atherosclerosis During the past year, Lewis & Page (319) reported the slow sedimenting lipoprotein of human serum in the ultracentrifuge to have the electrophoretic mobility of β-globulin, a lipoprotein, while in dog's serum, a slow sedimenting lipoprotein with the electrophoretic mobility of α-2-globulin could be demonstrated. Oncley, Gurd & Melin (320) also found about 70 per cent of the lipid of normal fasting plasma is present as β-lipoprotein It amounts to roughly 5 per cent of the total plasma proteins The purified material contains about 25 per cent protein, 30 per cent phosphatide, 45 per cent total cholesterol, with traces of other substances.

Gofman pointed out that giant lipoprotein molecules were found in sera of patients with myocardial infarction and atherosclerosis. These particles are demonstrated by measuring their rate of rise (negative sedimentation) from a medium of high specific gravity when subjected to ultracentrifugation. The rates of rise are recorded as S_f (Svedberg flotation) units In atherosclerosis, the particular molecular species has an S_f of 10 to 20 They are unrelated to the chylomicrons and to other macromolecules of greater density, S_f 3 to 8, which occur in all sera.

Gofman believes as a working hypothesis that these macromolecules are the cause of atherosclerosis or at least reflect the metabolic disturbance which itself causes the disease for the following reasons. (*a*) They are present in 97 per cent of patients who have recently had a myocardial infarct. (*b*) The distribution of positive blood tests between the normal male and female population is about what might be expected from the natural distribution of coronary disease, i e , a large preponderance of it in the younger male (20 to 40 years) age groups (*c*) Rabbits developing atherosclerosis from the feeding

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Angina Pectoris

By far the most significant contribution to this subject is that of Blumgart, Freedberg & Kurland (327) on the use of hypothyroidism produced by radioactive iodine in the treatment of euthyroid patients with angina and congestive failure. Hypothyroidism was induced to lessen the work of the heart and is proposed as a method of treatment for patients refractory to standard medical measures. Eight of thirteen patients with angina and three of five with congestive failure showed worthwhile improvement. The average total dose of I^{131} was 54 mc. An attempt is made to maintain the lowest metabolic rate consistent with the comfort of the patient. This group represents the intractable cardiac cripple who is ordinarily considered for surgery. There is little doubt in the reviewers' minds that in some cases important improvement has been produced and that the method is well worth extensive exploration

Disseminated Lupus Erythematosus

Two highly significant discoveries in the past two years are adding greatly to knowledge of this formerly completely obscure disease First, the discovery of a test by Haserick (328) based on the so-called "L. E. cell" by Hargraves, Richmond & Morton (338), which seems diagnostic of the acute disease state and even to give some indication of progress, and second, the discovery by Hench that cortisone and ACTH favorably affect the course of the disease. Klemperer *et al.* (329) have reported the presence of vivid, spindle shaped, hematoxylin-staining structureless bodies in a variety of tissues in 32 of 35 cases of lupus. They seem to originate in an alteration of the nuclei of mesenchymal cells. In some respects they resemble the Hargraves-Haserick LE cell from blood and bone marrow.

Baehr & Soffer (330) report on the treatment with cortisone and ACTH of five patients with lupus. Although they were dramatically improved, leucopenia, accelerated sedimentation rate, and persistence of LE cells indicate the disease was still active and the unknown cause had not been eradicated Schwartz & Somme (331) report partial success in the treatment of three patients with ACTH. Definite depression of serum globulin occurred and the formolgel reaction became negative.

Panarteritis Nodosa

While the results of interesting experimental work on animals have been published during the year, little that is new has appeared concerning the disease in patients. Rose, Littmann & Houghton (332) have presented an excellent pathological and clinical description of the disease

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DISEASES OF THE URINARY SYSTEM

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The present review encompasses the studies concerned with tuberculous infections, nontuberculous infections, nephrolithiasis, and neoplasms of the kidney and bladder. The various reports have been evaluated and correlated in an effort to present the prevalent trend of thought.

Tuberculous Infection of the Urinary Tract

Prior to the discovery of streptomycin, the treatment of renal tuberculosis consisted primarily of nephrectomy in certain selected cases. The remainder of the patients with tuberculous renal lesions received only nonspecific palliative measures (1). Positive medical regimens were not used because of the lack of effective antibiotic and chemotherapeutic agents and, more important, because of the lack of a clear concept of the pathogenesis of tuberculosis as a whole (2).

Medlar and co-workers (2), in an analysis of 5,424 necropsies on males over 16 years of age, have ascertained certain fundamental facts relative to the pathogenesis of renal tuberculosis; these facts are in agreement with the findings of previous workers. They (2) have demonstrated that renal tuberculosis is hematogenous in origin and is usually bilateral in its incipiency. The renal lesion is the local manifestation of a generalized disease. Contrary to older beliefs, small nondestructive tuberculous lesions of the renal parenchyma may heal spontaneously. On the basis of their data. Medlar *et al.* concluded that nephrectomy performed with the intention of either preventing spread of tuberculosis to other parts of the body or protecting the opposite kidney is an irrational procedure. Greenberger & Sporer (3) offer clinical and experimental data in support of the contention that nephrectomy in bilateral renal tuberculosis does not aid in the healing of the other kidney.

With the pathogenesis of renal tuberculosis in mind, and acknowledging the numerous data indicating that nephrectomy in clinical unilateral tuberculosis results in only 50 per cent survival five years after operation, Semb (1), Nesbit & Bohne (4), Ljunggren (5), and Lattimer (6) advocate a forceful medical regimen in the treatment of renal tuberculosis. Nesbit & Bohne (4) have suggested that all patients with renal tuberculosis be treated primarily with streptomycin and prolonged sanatorium care no matter whether the infection appeared to be clinically bilateral or unilateral They propose a 60 day trial period of strict bed rest and streptomycin therapy in unilateral tuberculous renal lesions. If, at the end of the trial period, the kidney shows evidences of healing by pyelography and/or guinea pig inocu-

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urines negative for acid-fast bacilli in 81 per cent of the patients while the 1 gm. dose produced negative urines in 58 per cent of the cases Eighty to one hundred per cent success in converting the urine has been obtained in patients with small renal lesions while only 40 per cent of the advanced renal lesions have been converted. Despite the fair success obtained with streptomycin in the advanced renal lesions, Lattimer advocates immediate (with a short course of preoperative streptomycin therapy) nephrectomy. The use of PAS (15) in conjunction with streptomycin has been suggested for future trial in renal tuberculosis

Nesbit (4, 13) has used a regimen of 2 gm. per day of dihydrostreptomycin for a period of 90 days; the course is repeated in those cases of bilateral renal tuberculosis and unilateral tuberculosis (patients having only one remaining kidney) whose urines have become positive for acid-fast bacilli after having turned negative during the first course of dihydrostreptomycin therapy

Romansky *et al* (16) have found a high incidence of delayed nerve deafness following dihydrostreptomycin therapy; this finding has not been substantiated (13, 17). The basic regimen employing dihydrostreptomycin has been dropped by the members of the Ninth Streptomycin Conference (18) for no obvious reason No remarkable difference was noted in the toxicity and therapeutic effectiveness of streptomycin and dihydrostreptomycin.

TB-1 (formylacetanilide, 3-thiosemicarbazone) was first synthesized by Mietzsch (19) and has been used extensively in Germany for treatment of urinary tract tuberculosis Hinshaw (20) reported that TB-1 is not as effective as streptomycin and appeared to be quite toxic A most recent report (18) on a pilot study upon TB-1 performed in the United States revealed a high percentage of liver dysfunction and blood dyscrasias. Therapeutic efficacy was not discussed

Many authors (6, 7, 8, 10, 11, 12, 21) indicate that streptomycin is of definite value in preventing miliary spread and aiding wound healing following nephrectomy when it is used pre- and postoperatively. Lattimer (6) advocates 2 gm per day for three days preoperatively and for three weeks postoperatively. At the present time great efforts are being made by members of the Streptomycin Conference to develop a regimen of streptomycin therapy which will be relatively nontoxic and therapeutically effective and will produce little incidence of bacterial resistance (18)

Nontuberculous Infections of the Urinary Tract

With the recent introduction of many new antibiotic and chemotherapeutic agents, the treatment of urinary tract infections has become a rather confusing matter for many physicians (22). The advent of these new adjuncts to treatment should not cause the therapist to abandon basic principles of diagnosis and therapy which have been well established (23) It is imperative that the physician follow a logical and orderly procedure both in the diagnosis and treatment of urinary tract infections Neglect in doing so may result in (*a*) development of bacterial resistance, (*b*) establishment of chronic

lation, then streptomycin therapy and bed rest is continued for 30 more days. Nephrectomy would be indicated at the end of the 60 day period if the kidney demonstrated so signs of healing.

Lattimer (6) is in agreement with the general regimen of streptomycin therapy and sanatorium care for cases with bilateral renal involvement and for those cases of unilateral disease in which there is little or no pyelographic evidence of renal destruction. If there is a gross ulcerating or cavitating lesion in unilateral disease, then nephrectomy, after a short preoperative course of streptomycin, is advised. Ljunggren (5) is in accord with Lattimer's regimen but utilizes *p*-aminosalicylic acid (PAS) instead of streptomycin.

Semb (1) suggests that the management of renal tuberculosis be organized with pulmonary tuberculosis as a pattern He advises mass efforts at early diagnosis, increased medical treatment, and individualized selective surgical therapy The surgical treatment of his cases has been carried out in a manner analogous with pulmonary tuberculosis Cases without evident renal destruction are treated with PAS and sanatorium care. Patients with local destructive kidney lesions have been treated with resection of the focus or partial resection of the kidney and those with total destruction, by nephrectomy. Semb has performed partial resections bilaterally in several cases of bilateral renal tuberculosis. Postoperative urinary fistula, spread of the disease, or bleeding have not been observed in the 14 patients undergoing the partial resections. Six cases have been followed for more than nine months, and five out of the six have negative urines.

Many urologists (7 to 11) still follow Albarran's concept and recommend nephrectomy in any type of unilateral renal tuberculosis, streptomycin being used only as adjunctive pre- and postoperative therapy.

Various chemotherapeutic and antibiotic agents have been employed both in the medical and combined medical-surgical regimens for treatment of urinary tract tuberculosis (5, 6, 12, 13) PAS has been used extensively in Sweden (5) in renal tuberculosis and appears to have produced a favorable response in some of the cases The follow-up period has been too short and the number of patients treated, too few for an accurate evaluation of PAS The Swedish investigators (5) employ PAS in a dosage of 8 to 14 gm per day for periods as long as six months More recently, they have combined PAS with streptomycin and chaulmoogra oil Some European investigators (5) have used calciferol and obtained beneficial effects

Slotkin (12) has conducted investigations on the combined use of diasone, moogrol, and streptomycin in the treatment of tuberculosis of the kidney He reported that 22 out of 23 patients observed for one year or less following therapy became abacilluric Inconclusive data to support the use of moogrol was reported by Schattyn (14); Lattimer (15) and Nesbit (13) have found that promizole and moogrol add nothing to the effectiveness of streptomycin while increasing the number of toxic reactions manifested by the patient

Lattimer (6, 15) has used streptomycin therapy in a relatively large number of patients with genito-urinary tuberculosis and has found 2 gm per day for 120 days to be the most effective regimen. This regimen produced

Sulamyd (sulfacetamide) has been found to be a very useful drug because of its low toxicity, marked solubility, and wide range of antibacterial activity (22, 36); the recommended dosage is 2 gm. per day. Sulfadiazine is quite effective in a dose of 4 gm per day (26), it gives a high blood level as well as a high urinary concentration. However, it produces a higher incidence of toxic reactions and is less soluble than sulfacetamide (36). Sulfisoxazole (gantrisin or Nu 445; 3,4,dimethyl-5-sulfanilamide-8-isoxazole) has been used extensively in the treatment of bacillary urinary infections and is reported by some investigators (37, 38) to have low toxicity and to have toxicity similar to sulfadiazine by other workers (39, 40). It is generally agreed that sulfisoxazole is quite effective against *Escherichia coli* and *Bacillus proteus* infections (37 to 40) in a therapeutic dose of 8 gm. per day; but its effectiveness in infections due to *Streptococcus faecalis* and *Bacillus pyocyaneus* is inconclusive at the present time. Recently, combinations of two or more sulfomamides in dosages less than the usual therapeutic dose of any one of the combined drugs have been investigated and found to be very efficient and of significantly lesser toxicity than any one of their separate constituents in equal or comparable dosages (36, 41) The use of combined sulfa compounds is based on the finding that the therapeutic actions of the compounds are additive while the solubilities and toxicities continue to be independent (22) Two of the combined sulfonamides available at the present time are sulfadial and tricumbisol. Some investigators (23, 42) have utilized sulfasuxidine and sulfathalidine in *E. coli* infections and found it to be fairly efficient and relatively nontoxic. It is not effective in other gram negative bacillary infections.

Penicillin is of no value in gram negative bacillary infections but is the drug of choice for the pyogenic coccal urinary tract infections with the exception of *S faecalis* (22). The most satisfactory method of administration has been the single daily intramuscular injection of 400,000 units of procaine penicillin-G (22)

If the primary course of therapy with the sulfonamides, penicillin, or penicillin plus sulfonamides is ineffective and if no pathological complication of the urinary tract is found on cystoscopy and retrograde pyelography, one then selects the next drug to be utilized on the basis of culture and *in vitro* sensitivity studies (22) Gram negative bacillary urinary tract infections are quite sensitive to streptomycin or dihydrostreptomycin (22, 27, 29 to 31, 43 to 45) Streptomycin is only occasionally effective in *Pseudomonas aeruginosa* and *S. faecalis* infections An adequate therapeutic dose of 2 gm per day for a period of five days should be utilized. Since bacterial resistance develops very rapidly, administration of any dose of streptomycin less than a therapeutic one will result in failure, even if the dose is increased at a later date (22, 29, 31, 45) Alkalinization of the urine with streptomycin treatment may enhance its therapeutic effectiveness (29)

Investigators (22, 46 to 51) have found aureomycin to be a very potent agent against both gram negative and gram positive organisms including *E. coli*, *Aerobacter aerogenes*, paracolon bacillus, *B. alcaligenes*, *S. faecalis*,

pyelonephritis, (*c*) failure in diagnosis of a concomitant serious disease, e g, obstructive uropathy or tuberculosis, and (*d*) unnecessary great expense to the patient (24).

In making the diagnosis of an infection of the urinary tract, it is necessary to perform an accurate examination of a carefully collected specimen of urine—a voided second glass specimen in the male and a catheterized specimen in the female (22, 24, 25, 26). The presence of infection is established on observation of pyuria and bacteriuria, pyuria alone, or solely bacteriuria. The most common finding in urinary tract infections is pyuria associated with bacteriuria. Pyuria without the presence of bacteria usually indicates either acid-fast infection or "amicrobic pyuria." Bacteriuria alone points to urinary stasis or a very low grade infection (22).

Primary therapy can be initiated on the basis of the stained urinary sediment without obtaining cultures (3) and sensitivity studies (22, 24, 25) If the infection fails to respond to the initial course of therapy, then the patient should have a complete urological examination with cultures for pyogens and acid-fast bacilli and *in vitro* sensitivity studies. Persistence of infection may be due to one of three factors (22): (*a*) the drug is ineffective against the prevailing organism, (*b*) complicating pathological entities (neoplasm, calculus, foreign body, obstruction) may be present, and (*c*) body resistance is so low that the usual defense mechanism cannot support the action of the drugs. It is widely recognized that complete cure of urinary tract infections cannot be accomplished with any of the known antibiotic or chemotherapeutic agents in the presence of pathological complications (22 to 33) Removal of foreign bodies, neoplasms, calculi, and urinary obstructions is an absolute necessity before complete cure of an urinary tract infection can be obtained.

If the infection clears with primary therapy, excretory pyelograms should be carried out (22, 25), since the urine may sometimes be temporarily sterilized with the administration of the newer drugs even in the presence of complicating pathological conditions

At the present time there is available to the therapist an imposing array of chemotherapeutic and antibiotic agents, e.g., sulfacetamide, triple sulfonamide combinations, sulfathaladine, sulfadiazine, gantrisin, sulfathiazole, mandelamine, neoarsphenamine, penicillin, streptomycin, aureomycin, polymyxin, chloromycetin, and terramycin. It has been found that 75 to 85 per cent of urinary tract infections are caused by gram negative bacilli (26, 29, 34) and that the majority of the gram negative bacilli are sensitive to the sulfonamides (22, 25, 26). In view of the preceding statement and the facts that sulfonamides are well tolerated, can be taken orally at home and are available at low cost, it has been suggested that one of the sulfonamides be the drug of choice in the primary therapy of bacillary urinary tract infections (22 to 26, 35). If the organism producing the infection is coccal in origin, then penicillin is the drug to be selected (22 to 26, 35). In cases of mixed infection of cocci and bacilli it is advisable to administer sulfonamides in conjunction with penicillin since some of the bacilli elaborate a penicillinase which renders the penicillin ineffective against the cocci (22, 24, 25, 26).

mapharsen, 0 04 gm. intravenously for the first dose and then 0 06 gm. on alternate days for the next six doses will usually clear the acute cases of abacterial pyurias (65). Ureterointestinal transplantation may be necessary for relief in the chronic case of abacterial pyuria (65)

Nephrolithiasis

The mechanism of formation of renal stones is still a highly controversial subject, and consequently, prophylactic medical therapy designed to prevent recurrence of calculi is also disputatious (66, 67, 68).

It is generally agreed that calcium phosphate and calcium oxalate calculi are, statistically, the most prevalent types of renal stones encountered (69 to 74). Other stones occurring less frequently are composed of uric acid, cystine, or xanthine. Prien (70), utilizing optical polarization techniques and x-ray diffraction photography, has analyzed 1,000 renal calculi and found that stones contain varied combinations of calcium, magnesium, ammonium, oxalate, phosphate, and urate; some of these forms have not been identified previously by routine chemical analyses

Numerous theories have been advanced to explain the mechanism of formation of calculi, but no one theory or combination of theories has been proven to be universally applicable (71) Some of the more popular proposals involve (*a*) changes in urinary colloids (68, 71, 84), (*b*) changes in urinary pH (68, 71, 83), (*c*) precipitation of crystalloids in urine due to supersaturation (68, 70, 71, 77, 79, 83, 84), (*d*) pathological lesions of renal papillae predisposing to crystalline deposition (70, 71, 73, 77), and (*e*) deposition of crystalloid upon a nidus (70, 75, 77)

Conditions which predispose to the possible activation of the previously mentioned mechanism are (*a*) metabolic defects, e g , cystinuria (85), uricaciduria (71, 74, 77), hyperparathyroidism with hypercalcinuria (68, 71, 74, 77, 80, 83, 86), (*b*) urinary tract and focal infections (68, 71, 76, 77, 87), (*c*) urinary stasis due to obstructive uropathy (67, 84), (*d*) hypercalcinuria due to hypervitaminosis D (68, 78, 83), recumbency with immobilization (81, 82, 88 to 91), active bone disease (68, 79), syndrome of hyperchloremic acidosis and nephrocalcinosis (92, 93), and (*e*) avitaminosis A (74, 77). Relatively few new facts have been added to the sum of knowledge concerning the relation of metabolic defects to calculous disease during the past three years. Satterthwaite (94) during World War II made the observation that there was an unusually high incidence of uric acid stones among the troops stationed in the Pacific theater This finding is quite interesting in view of the recent work demonstrating that uric acid excretion is increased under conditions of stress (Selye's Adaptation Syndrome) and with increased adrenal cortical activity (95)

In view of the high incidence of calcium phosphate and calcium oxalate renal calculi, most of the recent research has been directed toward elucidation of the causes of hypercalcinuria Dietrick (89) demonstrated in a series of normal young men that immobilization from the hips to the toes more than doubled the normal urinary excretion of calcium Whedon, Dietrick &

and *Streptococcus hemolyticus.* Most strains of *B. pyocyaneous* and *B. proteus* appear to be highly resistant. The oral therapeutic dose of aureomycin is 0.5 gm. every 6 hr. for a period of 10 to 14 days Toxic reactions are mild nausea and diarrhea.

An antibiotic somewhat similar to aureomycin in its effectiveness is chloromycetin (22, 52). It is administered orally in a dosage of 50 mg per kg. of body weight per day for a period of 7 to 14 days. Chloromycetin is devoid of gastrointestinal, neurotoxic, or allergic reactions. The drug was ineffective in all infections due to *P aeruginosa.* Unlike aureomycin, rapid development of resistance in certain strains of *B. proteus, B. alcaligenes,* and *A. aerogenes* has been observed with the administration of choromycetin.

Recently, Finlay and associates (53) have published a report about a new antibiotic named terramycin Terramycin has been used by several investigators (54, 55, 56) and found to have a wide range of antibacterial activity against both gram positive and negative organisms King *et al.* (55) administered terramycin hydrochloride orally in a dosage of 500 mg. every 6 hr. for five days and cleared urinary infections due to *A. aerogenes, E. coli, Streptococcus, B. pyocyaneus* and hemolytic *Staphylococcus aureus* It did not appear to be effective in mixed infections in which *Proteus vulgaris* was present. No recurrences of infection following cessation of therapy were reported However, Nesbit and co-workers (56) found that recurrence of infection with terramycin occurred not infrequently. They concluded that the antibiotic was a valuable addition to the armamentarium of the clinican treating urinary infections for it will cure some urinary tract infections completely refractory to all other antibacterials Terramycin is of relatively low toxicity and is well tolerated

Another antibiotic named polymyxin by American investigators (57) and aerosporin by British workers (58) has been found to have specific activity against gram negative organisms It is bactericidal in nature and acts most effectively against *P aeruginosa* and the coli-aerogenes group of organisms (33). Bacterial strains resistant to polymyxin have not been obtained under conditions which readily yield strains completely resistant to streptomycin (57) The recommended parenteral dose is 2 5 mg. per kg of body weight per 24 hr in divided doses Higher dosage will produce nephrotoxic and neurotoxic effects (33).

The advent of the many new antibacterials should not make the therapist lose sight of an older but still useful drug, methenamine mandelate. It has been found to have about the same range of activity as streptomycin and

lieved to be one of the manifestations of Reiter's disease by some workers (24, 62). The etiological agent is unknown at the present time (60, 61, 62) Neoarsphenamine in a dose of 0.3 gm intravenously on alternate days for three doses and 0.6 gm on alternate days for the next three to six doses or

of a stone, will accelerate and enhance the effect of crystalline solvents in the dissolution of renal calculi.

Medical regimens have been proposed for the dissolution of calculi as well as for postoperative prophylactic therapy (68, 74, 77, 83). The reports of the results obtained from the use of these regimens have been quite conflicting. Higgins (77) is one of the leading advocates of appropriate dietary regimens both in dissolution of calculi and in prophylaxis against recurrence of calculi This stems from his finding that exogenous sources play an important part in the formation of renal stones. Other workers (73, 79) feel that it is useless to attempt to control the incidence of stones by restricting foods containing substances of which the stone is known to consist, for the source of these substances is endogenous and not exogenous. The use of diets or chemical compounds to change urinary pH and thus prevent precipitation of crystalloids is also a highly controversial subject. Many workers (68, 74, 77, 84) advocate the utilization of an acid ash diet and/or ammonium chloride for the dissolution and prevention of calcium phosphate stones Prien (66), however, has found that apatite composes the nucleus of the great majority of phosphatic stones and that it can be deposited in calculi over a wide range of urinary pH, although the pure apatite calculi occur most commonly in a weakly acid urine In view of this finding, Prien questions the rationale of indiscriminate acidification of the urine of patients to prevent recurrence of phosphatic calculi. In addition, Cordonnier & Talbot (82) have found that acidifying drugs and an acid ash diet will often double and even triple the output of urinary calcium Because of this observation, they have advocated the use of sodium acid phosphate instead of ammonium chloride or an acid ash diet They demonstrated that sodium acid phosphate will produce a 50 per cent reduction in the urinary calcium excretion of patients and will lower the urinary pH

In the prevention of recurrent nephrolithiasis, practically all workers (67, 68, 72, 74, 77, 78, 80, 88, 91, 97) are agreed upon the following measures (*a*) eradication of urinary tract infections, (*b*) correction of urinary tract abnormalities leading to obstructive uropathy, (*c*) forcing fluids to insure a large volume of urine output, (*d*) prevention of immobilization, (*e*) correction of hyperparathyrodism, and (*f*) avoidance of administration of massive doses of vitamin D.

Neoplasms of the Kidney and Urinary Bladder

Neoplasms of the urinary tract manifest themselves most commonly by the sign of hematuria, and "it is now an accepted axiom that all cases of hematuria require an urologic investigation as to the source of the hematuria and its cause" (101) In addition to the utilization of the usual methods of cystoscopy and retrograde pyelography, cytological studies of the urine have been found valuable as an adjunct in the diagnosis of malignant tumors of the urinary tract (102, 103, 104)

Numerous classifications of renal tumors have been proposed in the past

Shorr (90) found that the hypercalcinuria of immobilization was markedly reduced by the use of an oscillating bed Recumbency is an important factor in the nephrolithiasis of spinal cord injuries (81, 82, 91) and osseous fractures Meyer & Mogensen (79) observed, in patients with osteo-articular tuberculosis, that calcium excretion was increased considerably during the active stages of the disease but not phosphorus or oxalic acid excretion.

Vitamin D in massive doses was found to produce hypercalcemia, hypercalcinuria, and tubular calcification by Addis and co-workers (78) Pyrah (83) caused calcification in rat kidneys in two to three days with large doses of vitamin D He also induced tubular calcification in cats by tying the pylorus This was done in an effort to reproduce experimentally the finding of tubular calcification in four patients with advanced pyloric stenosis associated with vomiting and dehydration; Pyrah postulates that the tubular calcification is caused by a marked alkalosis. He has found evidence in his rat experiments that calcified debris from the tubules may descend to the renal pelvis

Recent experiments by Conway, Maitland & Rennie (96) seem to disprove the theory that a deficiency of citrate excretion by the kidney is an important factor in the formation of renal calculi. They have shown that the apparent decrease in urinary citrate in patients with calculous disease is due to breakdown of the citrate by existing urinary tract infection with *E coli*, *S faecalis*, or *B pyocyaneus* and not due to some abnormality of the kidney metabolism. Patients with renal calculi and sterile urines excreted the same amount of citric acid as the normal individual.

The treatment of nephrolithiasis can be divided into surgical therapy and medical therapy Operative procedures will be guided by the patient's age, general health, renal function, symptoms, and physical type of calculus (77). Priestley & Dunn (97), in a statistical study of 382 patients, feel that staghorn calculi are best treated by nephrolithotomy rather than by nephrectomy or nonsurgical therapy Mayers & Campbell (98) report successful results with the use of partial nephrectomy or partial resection of the kidney in hydrocalyx, caliectasis, or similar entities containing calculi Harrison & Trichel (99) have found that the use of fibrin coagulum in pyelolithotomy is extremely useful in extracting small stones from renal pelves and calyces.

All patients with calculous disease should be completely investigated prior to any form of therapy (67, 68, 72, 74, 80, 84) The investigations should include blood and urine chemistry studies for signs of metabolic defects or excessive excretion of the crystalloids as well as bacteriologic study of the urine for infection (67) If a metabolic defect amenable to correction, e g, hyperparathyroidism, is encountered, treatment of the defect is carried out prior to surgical removal of the calculus (80)

Many stone-dissolving solutions have been administered either through ureteral catheters or nephrostomy tubes but have been found, in general, to be unsatisfactory (73, 91, 93) Keyser *et al* (100) offer presumptive evidence that the use of urease, by virtue of its digestant action on the organic matrix

Wilms' tumor is nephrectomy plus roentgen irradiation; some favor pre- and postoperative irradiation (119 to 123) while others (124) prefer post-nephrectomy irradiation only.

The etiology of most bladder neoplasms is unknown at the present time except for those tumors occurring in individuals with bilharziasis (125) and in workers employed in chemical factories (126). Ibrahim (125) has conducted an extensive survey in Egypt on bladder cancer and has arrived at the conclusion that bilharziasis is a potent cause of bladder neoplasm The greatest incidence of vesical tumors occurs between the ages of 30 and 39 in the class of individuals commonly infected with *Bilharzia*. The average duration of infection before the cancer is diagnosed is approximately 12 years. The neoplasm is usually inoperable at the time of treatment because the patients were unable to recognize the onset of the cancer which is masked in its early stages by the severe bilharzial cystitis

Beta-naphthylamine, a compound used extensively in the chemical industry, has been proven to be carcinogenic in dogs (126). Goldblatt (126) reviewed the incidence of bladder tumors in two chemical factories and found that the proportion of deaths at ages less than 45 years caused by occupational tumors of the bladder far exceeded that for all urinary tract tumors in the general population The mean period of discovery of the tumor was 18 95 years from the time of first entry into the industry. The statistical survey also indicated that the earlier the entrance into the industry, the earlier death was likely to occur if a tumor was contracted

The diagnosis of a bladder neoplasm can be made quite readily on cystoscopic examination, but its degree of malignancy is much more difficult to determine Dean (127) conducted a study on 100 cases of vesical neoplasm in which he compared the malignancy of bladder tumors as revealed by cystoscopic biopsy and as demonstrated by subsequent examination of the entire excised organ He found that 58 per cent of the cases showed differing reports when cystoscopic biopsy was compared with microscopic sections from the entire bladder He thus concludes that the successful treatment of bladder tumors depends on mature clinical judgment rather than on biopsy alone or bimanual palpation Because of the inadequacy of cystoscopic biopsy, Milner (128) has utilized the resectoscope to obtain tissue and has found [illegible] the tumor [illegible] ors to be of [illegible] to be in a better position to judge the potentialities of a bladder tumor than is the pathologist from its microscopic appearance. They state that the degree of neoplastic infiltration and site of the tumor are more important in determining the type of treatment. The depth of infiltration can best be estimated by bimanual palpation under general anesthesia (130, 131) Jewett & Lewis (130) have demonstrated the five year survival rate to be practically zero in cases of deeply infiltrating neoplasms despite cystectomy

The types of therapy in use at the present time can be classified as (*a*) medical, (*b*) roentgenological, (*c*) surgical, and (*d*) combinations of the three.

few years in an effort to increase the accuracy of prognosis. Foot and coworkers (105, 106) suggest that a classification based upon the embryologic origin of the tumor is the most reliable regarding correlation between pathologic findings and clinical outcome; entodermal tumors and those developing in mixed mesonephric rests bear an almost hopeless prognosis while mesodermal tumors offer a better outlook. Cahill (101) proposes that renal tumors be classified as parenchymal and pelvic tumors, the parenchymal tumors being further subdivided into clear cell carcinoma, granular cell carcinoma, true hypernephroma, tumors in solitary cysts, etc. and the pelvic tumors into papilloma, papillary carcinoma, squamous cell carcinoma, and undifferentiated carcinoma. Other workers (107) advocate a classification based on such histological criteria as degree of papillary or adenomatous formation, irregularity or variability of the cells, and the frequency of mitoses rather than the classification suggested by Cahill (101).

Beare & McDonald (108), in a study of renal parenchymal tumors, found that involvement of the perirenal fibrous capsule by tumor associated with perirenal venous dilatation offered a poor prognosis, while occurrence of either capsular or venous involvement alone was not associated with a material reduction in the five year survival rate

Early surgical removal of the involved kidney and perirenal tissue is the only known corrective procedure for renal parenchymal carcinoma (101, 107); irradiation therapy is of doubtful value. Mortensen (109) in 1948 reported a thoracoabdominal approach for the removal of large renal parenchymal tumors. The author believes that this method is excellent in that it avoids unnecessary trauma to the tumor, the pedicle of the kidney can be readily ligated before mobilization of the kidney, and all the perirenal tissues can be removed under direct vision with ease A similar approach has been used by other clinicians (101, 110 to 112) and found to be of great value Two new extraperitoneal procedures have been reported recently; one is a modification (113) of the Sweetser approach and the other involves the creation of an osteoplastic flap through a dorsolumbar extrapleural, extraperitoneal approach (114)

Papillomata and papillary carcinomata of the renal pelvis require removal of the kidney, ureter, and a cuff of bladder surrounding the ureteral orifice for possible cure (115 to 118). Nephroureterectomy is advised in the case of papillary renal pelvic tumors because many clinicians (116, 117, 118) have observed further tumor formation in the ureteral stump, intramural portion of the ureter, or in the bladder mucosa following nephrectomy alone.

Wilms' tumor, embryoma, or embryonal carcinosarcoma of the kidney is one of the most common carcinomas found in children (101) and until recently considered the most malignant of all renal growths The survival rate following nephrectomy for Wilms' tumor up to the year 1942 was less than 10 per cent. Irradiation was rarely used in the period covered by the reports giving low survival rates (119). Recent reports (120, 121) indicate that the cure rate may be increased to 50 per cent or more with the use of adequate irradiation and nephrectomy. Most authors agree that the best therapy for

not been satisfactorily eradicated (149, 161, 163). At the present time, the pendulum appears to be swinging back from cystectomy and ureterosigmoid transplants to radical transurethral resection of most bladder tumors (141, 143, 164).

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Medical therapy for bladder neoplasms is of rather recent origin and can be divided into the systemic and intravesical types. *Podophyllin in liquid paraffin* has been applied to vesical neoplasms transurethrally by Semple (132) and has been found to produce a diminution in the extent and size of papillomata. Harrison and co-workers (133) used stilbamidine systemically in two cases of extensive bladder carcinoma without any apparent beneficial effect. Some diminution in size of bladder neoplasms has been observed by Herbst & Bagley (134) with the administration of inositol. Lich & Grant (135) report disappearance of bladder papillomata with the use of oral stilbestrol.

Irradiation therapy for bladder cancers includes the well-established methods of deep external irradiation (136), radon seed implantation (137), and implantation of radium needles (138) as well as two new techniques (139, 140). Friedman & Lewis (139) have developed a procedure which entails the isoirradiation of the lower two-thirds of the bladder wall with gamma radiation by means of a small radium capsule held fixed in the center of the bladder by a Foley or Foley-Alcock catheter. Wallace, Walton & Sinclair (140) have also utilized the principle of intracavitary irradiation of the bladder mucosa but have used short-lived radioactive isotope, Na^{24}, as the source of the γ-rays.

Surgical procedures employed in the treatment of vesical neoplasm are transurethral resection (141, 142, 143), transurethral fulguration (144), segmental or partial resection of the bladder wall (127), total vesical resection with ureterointestinal anastomoses (145), and cystectomy with ureterocutaneous transplants (146)

From the numerous therapeutic procedures previously outlined, it can be deduced that the treatment of bladder cancer is rather unsatisfactory. The indications for the use of a particular procedure are quite varied (127, 143, 145, 147 to 149) and are difficult to standardize in the light of our present knowledge and experience Most clinicians are agreed upon the fact that the papilloma and the very superficially infiltrating solitary neoplasm can be treated quite adequately by most of the conservative procedures (150) Deep external irradiation has been reserved for elderly patients with far advanced bladder neoplasm (127, 148) Treatment for the group of neoplasms which are classified between the two extreme groups previously mentioned has been very unsatisfactory irregardless of the type of procedure employed.

With the advent of antibiotic and chemotherapeutic agents, there has been a marked swing to the use of cystectomy and ureterointestinal transplants for Grade II, III, and IV bladder carcinoma (130, 131, 147, 151 to 154). New and revived ureterosigmoidostomy techniques (155 to 159) have been proposed in the past few years in an effort to decrease the hydronephroses and pyelonephritis which were prone to follow ureterosigmoid transplants performed previously. However, recent reports indicate that pyelonephritis (160), hyperchloremia with acidosis (161, 162), and hydronephrosis are still prevalent despite modern measures. In addition, vesical cancers have

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DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HEMATOLOGY[1]

Hemorrhagic and Leukocytic Diseases

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One cannot help but be impressed and perplexed by the current scope of hematological research. New instruments and techniques have extended cell morphology into structural regions considered submicroscopic. Plasma fractionation and observations of protein interaction, employing the disciplines of physical chemistry, have contributed to our knowledge of blood coagulation. Biochemical studies of nucleic acid metabolism appear important in the understanding of the abnormal growth processes of leukemia. Biophysical tracer methods and immunochemistry have likewise found important application in hematology. A review article can do little more than reflect broad currents of investigative interest and attempt to correlate them with the practical problems which face the clinician Carpenter (213), in the first volume of the *Annual Review of Medicine*, has reviewed the erythrocyte and anemia This chapter will, therefore, be concerned with blood coagulation and the hemorrhagic diatheses and with the leukocyte and leukocyte disorders

Blood Coagulation and the Hemorrhagic Diatheses

Extensive discussion of the mechanism of blood coagulation may be found in the current literature (1 to 6) Recent studies have indicated hitherto unsuspected complexities However, a closer approximation has been reached between clinical problems of hemorrhagic disorders and the laboratory demonstration of specific hemostatic defects More than anything else, the prothrombin test has provided the means of attacking these problems. Through various modifications in the prothrombin test, it has been possible to dismember the coagulation mechanism into several component parts which may be quantitatively measured Such tests may be found in Ham's syllabus (7) and in articles by Stefanini (8) and Owren (9) It seems appropriate to organize recent experimental observations according to the general areas of blood coagulation in which they fall, that is, the platelet, the antihemophilic globulin, prothrombin, and accelerator factors, and various anticoagulants. For purposes of the following discussion, a simplified scheme of blood coagulation, which includes these substances of clinical importance, may be summarized in three sequential reactions. In the first reaction of

[1] This review covers approximately the period from 1945 to July, 1950.

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of normal platelets after transfusion, presumably derived from the donor blood. Approximately 20 per cent of the transfused platelets were accounted for in the circulating blood, and they survived for five or six days.

The morphological characteristics of the megakaryocyte have been of interest in thrombocytopenic purpura, since it is generally accepted that platelets are derived from the cytoplasm of this cell. Girdwood (22) states that the dry syringe technique is superior to the use of anticoagulants in the demonstration of platelet budding. Fixed preparations are preferable for quantitating the number of megakaryocytes (23) In idiopathic thrombocytopenic purpura, there appears to be a normal or increased number of megakaryocytes in the marrow, but platelet formation as evaluated by granularity of cytoplasm, and platelet budding is reduced (24 to 28). Whether there are other cytologic changes, such as an increase in immature megakaryocytes, is a matter of debate.

In a review of the clinical picture of thrombopenic purpura in pregnancy, Epstein, Lozner & Cobbey (29) found a maternal mortality of 8 7 per cent and an infant mortality of 26 1 per cent They suggest that a transplacental passage of an immune body would account for the disease in the infant McAlenney & Kristan (30), in a study of 42 cases of thrombocytopenia in the newborn, point out that the mortality was 42 per cent in the group with associated purpuric manifestations in the mother and only 6 per cent in those children without such a maternal history In those infants surviving, spontaneous recovery occurred within a few days

Evans & Duane (31) stress the association of acquired hemolytic anemia and thrombocytopenic purpura, and they suggest an abnormal immune mechanism producing both.

Ackroyd (32) reports three cases of thrombocytopenic purpura following rubella Circulating platelets were depressed to hemorrhagic levels, but there was no evidence of megakaryocyte damage in the marrow Evidence is presented to indicate that mild depressions of platelets are not uncommon in rubella and in other infections, regardless of their severity The same author (33) discusses the mechanism of thrombocytopenia occurring with sedormid therapy. In sensitive patients, agglutination of the platelets and a reduction in the clot retraction were produced *in vitro* by sedormid. It was also possible by the topical application of the drug to produce local hemorrhage in two of three patients

There have been numerous reports of a syndrome characterized by fever, hemolytic anemia, and thrombotic thrombocytopenia (34). Histological examination revealed platelet thrombi in small vessels throughout the body. These would appear to account for the neurological findings, reviewed by Adams *et al* (35), which include muscle weakness, dizziness, confusion, convulsions, stupor, and coma All cases have been fatal The anemia is unaccompanied by evidence of autoimmunization, and in three instances, splenectomy did not alter the fatal outcome (36)

blood coagulation, platelets and antihemophilic globulin are needed for formation of thromboplastin; in the second stage, thromboplastin plus prothrombin and accelerator factors result in thrombin formation; in the third stage, fibrinogen is converted to fibrin through the action of thrombin.

The platelet and thrombocytopenic purpura.—Classical methods of evaluating the platelet and its function include the platelet count, bleeding time, clot retraction, and capillary fragility tests Aggeler, Howard & Lucia (11) emphasize the difficulties of the platelet count and delineate the general usefulness of these other tests in thrombocytopenic purpura. While these measurements clearly indicate the importance of platelets, it has been difficult to demonstrate their specific function in blood clotting. Overcoming the technical difficulties in obtaining a platelet-free plasma, Conley, Hartmann & Morse (10) have demonstrated the necessity of both platelets and a plasma factor for normal thromboplastin formation.

The prothrombin consumption test has been devised as a means of evaluating platelet function (12 to 15) This test consists of measuring the quantity of prothrombin in blood before and after clotting, i.e., the difference represents the amount of prothrombin consumed In the clotting process, thromboplastin and prothrombin react to form thrombin. Since this reaction is considered stoichiometric, the amount of thromboplastin formed is equivalent to the prothrombin consumed Thromboplastin formation depends on functional platelets and antihemophilic globulin. The prothrombin consumption test may thus be used as a measure of the function of either of these components if the normalcy of the other is established While Owren (17) suggests that the prothrombin consumption test actually measures the decrease of a substance other than prothrombin, the usefulness of the test in determining the functional capacity of the platelet mass is valid in thrombocytopenic purpura (13 to 16) Observations of this type would be of particular interest in thrombasthenia Hirsch *et al* (18) report a patient with a bleeding diathesis and large platelets which were nonfunctional in terms of prothrombin consumption Alexander & Landwehr (19) report similar measurements on a patient with the clinical picture of thrombocytopenic purpura, a prolonged bleeding time, but a normal platelet count. These platelets were shown to be nonfunctional on the basis of the prothrombin consumption test

The life span of platelets was measured by Lawrence & Valentine (20). Cats previously made thrombopenic by irradiation were cross-circulated with normal animals After the cross-circulation was discontinued, the rate of fall of the circulating platelets was approximately 2,500 per cu mm. per hr. This would indicate a turnover of platelet mass every two to five days if these results may be applied to the normal animal. In man, attempts to increase the level of circulating platelets by transfusion have not been successful (21). However, Hirsch and associates (18), in a patient with thrombopathic thrombocytopenic purpura, were able to demonstrate the presence

thrombin might well be expressed as "prothrombic activity" since one is measuring a complex system dependent upon a number of factors. Ware & Seegers (53) describe a simplification of their two-stage method; accelerator globulin is added so that this will not be a limiting factor in measuring the prothrombin content of plasma The one-stage method of Quick has proved most convenient for clinical purposes. While this method may be affected by a deficiency of either labile factor or fibrinogen, these may be added, as in Owren's modification (54).

Prothrombin appears to have a rapid turnover in the plasma In the dicumarolized rabbit, 50 per cent of the administered prothrombin disappears within 12 hr. (55). A similar rate of fall was observed in rats by Mann *et al* (56) when the absorption of vitamin K_1 was prevented by an intestinal lymph fistula. In one patient with congenital hypoprothrombinemia, Landwehr *et al* (57) found a still more rapid disappearance rate of transfused prothrombin.

Water soluble vitamin K preparations (Hykinone, menadione, Synkavite) are effective in the treatment of hypoprothrombinemia due to a deficiency of vitamin K (58). In the treatment of dicumarol toxicity, however, these materials may have a negligible effect, whereas vitamin K_1 and K_1 oxide are effective in raising the prothrombin concentration above hemorrhagic levels in 12 to 24 hr. (59, 60). A recently developed emulsion of vitamin K_1 is suitable for intravenous injection (61). Neither water nor oil soluble preparations appear to be effective in idiopathic hypothrombinemia or with severe disease of the liver parenchyma.

Several groups of workers have identified accessory clot-promoting factors which increase the rate of conversion of prothrombin to thrombin. In plasma, these have been called plasma accelerator globulin by Murphy *et al.* (62), labile factor by Quick & Stefanini (63), and accelerator factor by Fantl & Nance (64). In serum, a factor active in the conversion of prothrombin to thrombin has been designated serum accelerator globulin by Ware & Seegers (65), Factor VI by Owren (9), serum prothrombin conversion accelerator by DeVries, Alexander, & Goldstein (66), and serum prothrombin converting factor by Jacox (67) Certain differences in the chemical and physical properties of these plasma and serum factors have been described by the different investigators At the present state of our knowledge, it seems likely that there may be a common identity of the various described plasma factors as a group, and the process of blood clotting converts the plasma factor into a more active serum moiety

Reports of idiopathic hypoprothrombinemia before the recognition of these auxiliary prothrombin conversion factors did not indicate whether such patients had a true deficiency of prothrombin or of prothrombin accelerator It has been possible by modifications of the prothrombin test to measure each factor separately. True idiopathic hypoprothrombinemia, usually familial, has been established in a number of instances (66, 68, 69). Likewise, there have been reported cases in which there was a deficiency of

Antihemophilic factor.—The studies of Lozner & Taylor (37) indicated that a globulin of importance in blood coagulation was decreased or absent in hemophilia. By high speed centrifugation, Chargaff & West (38) have demonstrated a deficiency in hemophilia of a clot-promoting factor similar to tissue thromboplastin. The prothrombin consumption test likewise indicates a deficient production of thromboplastin not attributable to platelet dysfunction (12, 13, 14). While there may be a defective ability to mobilize thromboplastin rather than an absolute deficiency of precursor (39), recent studies embrace the concept of inadequate thromboplastin formation in hemophilia. Graham and his associates (39) reported on "canine hemophilia" which appears to be similar to the human disease in genetic, clinical, and therapeutic aspects.

An antihemophilic globulin has been localized in Fraction I and in Fraction II plus III of Cohn and associates. Fraction I is effective *in vivo* and *in vitro* in reducing the clotting time of hemophilic blood (40, 41, 42). Amounts of 100 to 400 mg resulted in a fall in the clotting time from 100 min to between 10 and 20 min, the effect lasting for one to four days (43). While fresh plasma has been more potent than preparations of Fraction I in general, this may be ascribable to the use of old plasma for fractionation.

The practical problem of management of the hemophilic patient has been discussed by Davidson *et al* (44) and by Wright and associates (45) The local application of thrombin has proved helpful for external bleeding (44). Maximum effect on clotting time may be obtained by transfusion of from 50 to 100 ml. of fresh or frozen plasma (45). Surgical procedures are still a serious undertaking despite all therapeutic adjuncts (46).

The use of repeated transfusions in hemophilia has produced a refractory state to further therapy in some patients. Munro (47) reported the presence of a circulating anticoagulant in such a case Craddock & Lawrence (48) reported two similar cases in which there was a positive precipitin reaction against the antihemophilic globulin Frommeyer *et al* (49) found that 5 of 22 hemophiliacs showed clinical and laboratory evidence of refractiveness to therapy.

These antibodies against antihemophilic globulin which develop as a result of transfusion therapy may further prolong the clotting time of the hemophilic patient. Their effect may temporarily be overcome by massive blood administration, presumably accomplished by the temporary exhaustion of circulating antibodies (49)

Prothrombin and prothrombin accelerators —Highly purified preparations of prothrombin have been prepared by Seegers and associates (50) However, there are no properties which allow its direct quantitative measurement; rather, prothrombin must be estimated by thrombin formation and the resultant conversion of fibrinogen to fibrin Different calibration curves (prothrombin concentration versus time) are obtained with different preparations of thromboplastin and with different plasma diluents (51) As suggested by Alexander, DeVries & Goldstein (52), measurements of pro-

marized the pharmacology and clinical usage of heparin and dicumarol. New anticoagulants have been given clinical trial. Burt *et al.* (93) and Solomon *et al* (94) compared the action of bis-3,3'-(4-oxycoumarinyl)-ethyl acetate (Tromexan) with dicumarol. The former was found to be less active than dicumarol but produced a more rapid fall of prothrombin and a more prompt recovery resulted with cessation of therapy. Phenylindandione has been used by Gueguen & Soulier (96) and by Blaustein *et al.* (97). This appears also to act more rapidly than dicumarol On the other hand, 4-hydroxycoumarin No. 63 [2-methyl-2-methoxy-4-phenyl-5-oxodihydropyrano-(3,2-C)-1-benzopran] was reported to be several times more potent than dicumarol with a longer period of activity (95, 97). Preliminary studies by Sorenson & Wright (98) on sodium polyanhydromannuronic acid sulfate (Paritol) indicate that this drug, similar in action to heparin, may provide a less expensive substitute in anticoagulant therapy.

The Leukocyte and Its Leukopathies

In the recent literature relating to leukocytes, there has been a preoccupation with the problem of leukemia and particularly with the chemotherapy of leukemia. In an attempt to understand the abnormal growth processes characteristic of leukemia, the limitations in knowledge of normal leukocyte behavior become apparent. This has served as a stimulus for morphological and physiological studies of the leukocyte

Methodology and morphology—The isolation of the viable leukocyte from the other formed elements of the blood has been accomplished by utilizing the differences in the specific gravity, or by agents promoting rouleaux formation of the erythrocytes (99 to 102) By increasing the concentration of fibrinogen in blood to between 6 and 7 mg. per ml of blood, Buckley, Powell & Gibson (103) have obtained yields of from 75 to 85 per cent of the total white cells in the blood by differential sedimentation Such methods show promise of separating formed elements of blood, much as plasma has been fractionated. By the isolation of appreciable quantities of leukocytes, it will be possible to conduct chemical, enzymatic, and isotopic studies on white cells which have hitherto been impractical.

In experimental and clinical hematology, the advantages of marrow examination as a supplement to peripheral blood studies have become recognized and are well summarized in Leitner's monograph (104) Iliac crest and spinous processes have proved to be as suitable as sternal marrow sampling and are potentially less hazardous (105, 106) Difficulties have resulted from the interpretation of marrow aspirations because of the different types of preparations made While marrow smears are superior for the demonstration of qualitative cell changes, fixed tissue preparations from aspirated marrow fragments permit recognition of granulomatous lesions found in tuberculosis, sarcoidosis, brucellosis, and, recently described, in infectious mononucleosis (107) As demonstrated by Berlin *et al.* (108), the total nucleated cell count is unreliable as an index of marrow cellularity,

labile or plasma accelerating factor (9, 69, 70). Crockett *et al.* (71) describe a patient in whom administration of serum as well as plasma was effective in reducing the prothrombin time. Plasma accelerator factor is normal in patients with hypoprothrombinemia due to inadequate absorption of vitamin K, but it is decreased with dicumarol therapy or with parenchymal liver disease (72). Stored blood has been shown to undergo a loss of labile factor rather than a loss of prothrombin activity (73).

Circulating anticoagulants.—Hemophilic-like syndromes are being identified with increasing frequency as being due to specific anticoagulants Conley, Hartmann & Morse (74) describe techniques for the detection of such anticoagulants and, in clinical studies, identified eight instances in which a circulating anticoagulant was responsible for the hemorrhagic diathesis A number of workers (47 to 49, 75, 76) have identified anticoagulants active against the antihemophilic globulin Other reports indicate anticoagulants which prevent the formation of thromboplastin and its activation of prothrombin (38, 47, 77 to 80) Fantl & Nance (81) and Harrington *et al.* (82) describe circulating anticoagulants active against the thromboplastin of human brain, but not that of rabbit brain. Of 17 patients with circulating anticoagulants, 10 were true hemophiliacs who had received numerous transfusions, 3 were women whose hemorrhagic disease seemed related to parturition. There were three elderly males and one female who had never received blood. Dreskin & Rosenthal (75) emphasize the possible role of immunization through pregnancy in the women afflicted In one patient, Conley *et al* (79) describe an anticoagulant preventing the conversion of prothrombin to thrombin.

Allen & Jacobson (83) describe the presence of an anticoagulant in the blood of experimental animals following irradiation. This anticoagulant was measured by the titration of heparinized blood with protamine or toluidine blue. An increased amount of protamine required to clot blood was taken to indicate the presence of heparin-like substances These authors and others 84 to 89), on the basis of the protamine titration, have reported an increase in heparin-like substance following nitrogen mustard therapy, in thrombocytopenic purpura, and in other miscellaneous conditions associated with a bleeding tendency. They report that the platelet depression did not correlate with the protamine titration (90) and was therefore independent of it. In some patients, the hemorrhagic tendency could be temporarily counteracted by the intravenous administration of protamine or toluidine blue, but results do not appear to be consistent. The importance of the heparinoid substances and their exact identity at present is not clearly defined Cronkite (91), while observing the prolongation of the clotting time in some animals exposed to ionizing irradiation, reports that the usual phenomena responsible for bleeding were (*a*) increased vascular fragility, (*b*) thrombopenia, and (*c*) ulcerations.

A discussion of the use of anticoagulants in the treatment of thromboembolic disease is beyond the scope of this article. Riggs (92) has summa-

active phosphorus, the leukocytes were localized predominantly in the lungs. Bierman and associates (124), employing interarterial cross-transfusion in man, also obtain data indicating that the lungs are capable of removing large numbers of leukocytes from the circulation. Lawrence *et al.* (125), in cross-circulation studies in cats made leukopenic by x-ray, found a disappearance rate of 888 cells per cu. mm. per hr. or a postulated turnover of the white cell mass of 1½ times in 24 hr.

A number of factors appear capable of influencing the level of circulating leukocytes Tullis (126) found that the granulocytes were better preserved *in vitro* in hypertonic solutions in comparison with hypotonic solutions for plasma cells and lymphocytes. In animals, hypertonicity was associated with an increase in the circulating granulocytes (127), and a positive correlation was found in diabetic acidosis between the hyperosmolarity of the plasma and the degree of leukocytosis (128)

Endocrinopathies have been observed to be associated with significant alterations in the level of the formed elements of the blood (129, 130, 131) Of particular interest at the present are the changes produced by the adrenal steroids Stimulation of the adrenal by adrenocorticotrophic hormone (ACTH) results in leukocytosis, lymphopenia, and eosinopenia (132). These are the result of the oxysteroids of the adrenal (compounds E and F). Enumeration of the eosinophils by direct counting methods (132, 133) has proved to be a useful index of adrenal activity A test devised to evaluate the functional integrity of the adrenal consists of determining the fall of eosinophils 4 hr after the intramuscular injection of ACTH (134) In Addison's disease, this fall is negligible, while a reduction of over 50 per cent occurs in the normal individual. The fall in eosinophils after the injection of epinephrine may be used to test the functional integrity of the pituitary-adrenal axis. Studies by Hume & Wittenstein (135) would indicate that epinephrine and other neurogenic stimuli act on the hypothalamus which in turn stimulates the pituitary to liberate ACTH. However, the ingenious studies of McDermott *et al* (136), in which pituitary tissue was transplanted to the anterior chamber of the eye, would indicate that epinephrine may act directly on the pituitary The pattern of blood changes after ACTH or epinephrine is similar to those produced by a great variety of stress situations as discussed by Selye (137). The failure of these changes under stress has been used to detect adrenal insufficiency Roche *et al* (138) report the marked fall in eosinophils postoperatively and describe a patient with adrenal insufficiency where this fall failed to occur Faloon *et al.* (139) describe a patient with meningococcemia where the eosinophil count provided a useful index for treatment of adrenal insufficiency.

Valentine and associates (140) summarize the effects of adrenal steroids on lymphoid tissue and the circulating lymphocytes. That the lymphocyte is the sole seat of antibody production and that dissolution of a lymphocyte results in the liberation of antibodies, as proposed by Dougherty, Chase &

due to the variable dilution by peripheral blood. However, when the total marrow count is five times the peripheral blood count, the differential marrow count is a reliable index of the marrow pattern. In a comparison of total cellularity of the marrow by nucleated cell count and by pathological section, Weisberger & Heinle (109) found great discrepancies in some instances In general, there was better correlation when the marrow was hypoplastic.

Block & Jacobson (110) discuss the technique of splenic puncture in which they employed a transthoracic approach. This procedure was particularly helpful in distinguishing atypical leukemia or lymphoma and myeloid metaplasia from conditions of hypersplenism in which splenectomy was indicated. While splenic puncture furnished information of value in certain cases, the hazard is evident from the occurrence of serious hemorrhage in 4 out of 55 patients.

The phase microscope (111, 112, 113) and electron microscope (114) have provided new possibilities of visualizing structural components of the leukocyte, although their use is still in its infancy. Histochemical techniques have made possible the measurements of various cell constituents, such as glycogen (115), lipids (116), and phosphatase (117). By the use of an ultraviolet microspectrographic technique, Thorell (118) has analyzed quantitatively certain cytochemical processes in hematopoiesis The formation of new cell protein was associated with a high concentration (greater than 5 per cent) of ribose polynucleotides in the cytoplasm and nuclear apparatus During maturation, the ribose polynucleotide decreased to 0 to 0 5 per cent parallel with the decline in growth activity of the cell Acute leukemia was characterized by a measurable hypertrophy of ribose polynucleotide metabolism.

In 1949, Hargraves (119) described the lupus erythematosis (LE) cell which consists of a large, homogenous, purple (Wright's stain) inclusion body in the granulocytes This mass is inferred to be nuclear material since it stains with Feulgen reagent LE cells are found in marrow drawn in anticoagulant from a patient with disseminated lupus erythematosis, or after exposing normal marrow or peripheral blood to the serum of a patient with disseminated lupus erythematosis. Berman *et al.* (120) feel that 10 or more LE cells are strong evidence for the diagnosis of lupus erythematosis Haserick & Lewis (121) have demonstrated that this phenomenon occurs in the presence of a globulin found in the blood of these patients but not in normal serum

Leukocyte physiology—In contrast to the precise information concerning the production and the destruction of the red cell, very little is known about the life span of the leukocyte Dreyfus (122) reports, as have others, that transfused leukemic cells disappear within minutes of transfusion Weisberger *et al* (123) found that leukocytes transfused to rabbits disappeared almost at once, and by histological studies and tagging with radio-

bone marrow and hyperfunction of the spleen Unfortunately, this is often impossible. The cardinal features of splenic hyperfunction as listed by Kracke & Riser (164) include: (*a*) splenomegaly (the single exception being essential thrombocytopenic purpura), (*b*) depleted cell values in the blood (neutropenia, thrombopenia, anemia, or any combination of these), (*c*) demonstration of the morphological integrity of the marrow, and (*d*) demonstration of splenic overactivity by the epinephrine test.

Reimann & de Berardinis (165) have reviewed 16 cases of periodic cyclic neutropenia in which no etiological factor could be established From the marrow changes, it appeared that the neutropenia was due to a decreased formation of leukocytes Splenectomy appeared somewhat beneficial in four instances, but was of no effect in two. Chronic agranulocytosis is discussed by Adams & Witts (166). They regard the cases which they report as a variant of aplastic anemia in which the impact of the damage is on the white cells. Four of their five patients were women. Only one patient died within five years in contrast to a predicted mortality in aplastic anemia of 60 per cent in two years The marrow was either hypo- or hypercellular, but with a decrease in the mature granulocytes. The spleen was not appreciably enlarged, and splenectomy was without effect Hickie (167) demonstrated a lack of bactericidal power of the blood of a patient with chronic agranulocytosis The serum of this patient appeared to be antagonistic to normal neutrophil activity.

Severe leukopenia has been reported with miscellaneous diseases of the spleen such as Gaucher's disease (168), Banti's syndrome (169), reticuloses (170), and associated with arthritis (171), A second group of reports deals with splenic leukopenia or pancytopenia unassociated with other diseases (172, 173) All of these are felt to be due to hyperfunction of the spleen, since splenectomy is effective in returning the white count to normal. Heinle & Holden (173) describe seven patients with primary splenic panhematopenia in whom neutropenia was the outstanding feature. Six were remarkably improved by splenectomy, while one died

The term hypersplenism appears well established whether with or without other disease (secondary or primary) Doan has reviewed the various conditions grouped under the heading of hypersplenism (174) He supports the hypothesis that cellular elements are destroyed by the spleen, in contrast to the idea, as expressed by Dameshek & Estren (175), of inhibition of the bone marrow by the spleen

Malignant leukopathies.—As discussed by Merskey (176), the line of differentiation between leukemia and such conditions as nonleukemic myelosis is poorly defined Examination of the marrow has been helpful in the diagnosis of leukopenic leukemia and particularly so in multiple myeloma (177) Kolff & Dhont (178) emphasize the triad of diffuse increase of plasma cells in the marrow, hyperglobulinemia, and primary amyloidosis in the diagnosis of multiple myeloma However, diffuse plasmacytosis of the marrow

White (141), would seem unlikely. Fagreus (142) presents persuasive evidence connecting the plasma cell with antibody production Proliferation of plasma cells correlated with antibody formation and distribution of both antigen and antibody correlated better with plasma cell distribution than with lymphoid tissue as a whole. Keuning & van der Slikke (143) found antibody production in both white and red splenic pulp. They conclude that antibody production is accomplished by both immature plasma cells of the red pulp and by lymphoblastic cells of the Malpighian corpuscles, but not by mature lymphocytes.

The role of the adrenal in the white cell response to infection and to the *leukocyte-promoting factors of Menkin (144) is not clear. There is suggestive* evidence that the adrenal is not the only mechanism involved in the leukocyte response following the injection of a pyrogen (145).

Benign leukopathies.—Further clinical manifestations of infectious mononucleosis have been described, particularly the frequent incidence of liver dysfunction (146) which may progress to cirrhosis (147). Associated neurological manifestations summarized by Dolgopol & Husson (148) include polyneuritis and encephalitis Thrombocytopenic purpura (149) and hemolytic anemia with a positive Coomb's test (150) have been described There is no convincing evidence that newer antibiotics influence the underlying disease (151). A convenient, rapid, slide agglutination test with sheep cells has been devised by Moloney & Malzone (152).

New drugs have been reported to produce agranulocytosis These include propylthiouracil (153), pyrethyldione (Presidon) (154, 155, 156), certain of the antihistaminics [tripelennamine (Pyribenzamine) (157), and, perhaps, metapheniline (158)] the antiepileptic drugs [trimethadione (Tridione), *methylphenylethylhydantoin (Mesantoin), and paramethadione (Paradione)* (159], and perhaps chloramphenicol (Chloromycetin) (160). As has been described with the sulfonamides and uracil derivatives, the antiepileptic drugs may produce either a neutropenia or a severe pancytopenia.

With the increase in exposure to irradiation, the hematopoietic changes produced have been of considerable interest Liebow, Warren & DeCoursey (161) report on the marrow changes in atom bomb casualties. Massive destruction of the myeloid tissue was followed by hyperplasia of reticulum and plasma cells with an increase in the marrow lymphocytes. Hypercellular marrows with peripheral pancytopenia occurred as late sequelae. Dickie & Hempelmann (162) have described neutral red bodies in lymphocytes which, although nonspecific, *may be used as an index of exposure to irradiation.* Lawrence and associates (163) have investigated the effect of x-ray on the circulating blood. They found no evidence of an indirect effect, the changes which occurred in the circulating white cells were consistent with those produced by adrenal hyperfunction following stress.

In considering leukopenic and agranulocytic syndromes of unknown etiology, one attempts to distinguish between primary dysfunction of the

per cent (194). Leukemia in childhood is more frequently affected favorably than is acute leukemia in adults. The remissions are usually of a few days or weeks in duration, in general somewhat shorter than those observed with folic acid antagonists. A second course of ACTH or cortisone is usually not effective The mode of action of oxysteroids and folic acid antagonists would appear to differ, since a refractory state to one does not preclude a remission induced by the other. While little practical value can yet be claimed for the use of oxysteroids in acute leukemia, the effect of a substance naturally occurring in the body is of great interest and merits further investigation.

Roentgen therapy—In chronic leukemia, roentgen therapy would still be the treatment of choice, since it allows either generalized therapy (spray irradiation) or localized treatment of tissue masses When generalized irradiation is preferable, radioactive phosphorus (P^{32}) may be considered equally effective and has the advantage of not producing irradiation sickness (195, 196). In chronic leukemia, the aim of therapy is primarily to keep the patient symptom-free. Osgood (197), on the basis of eight years of experience, believes that this can best be accomplished by small maintenance doses of x-ray or P^{32}, regulating the white count between 10,000 and 20,000.

X-ray therapy in multiple myeloma is effective only when the process appears localized (198) While stilbamidine has been reported to alleviate the pain in some instances (199), the over-all results are discouraging Lawrence & Wasserman (200) report treatment of 24 patients with P^{32} and radioactive strontium (Sr^{89}) Moderate symptomatic improvement was observed in five cases. Loge & Rundles (201) reported improvement in four patients on urethane therapy. Harrington & Moloney (202) observed remissions in 6 of 11 cases on urethane There is some indication that ACTH and cortisone may affect the more immature type of myeloma (194).

Urethane.—The use of urethane was first reported in the treatment of leukemia by Paterson *et al* (203) after experimental observations had indicated a growth-inhibiting effect on animal tumors In addition to its effectiveness in myeloma, it has proved a useful form of therapy in chronic myelogenous leukemia (204) The ethyl carbamate has proved the most effective of the various carbonamide derivatives studied (205)

Nitrogen mustard—Methyl-bis-(β-chlorethyl)-amine hydrochloride (nitrogen mustard) is of value chiefly as an adjunct to x-ray in the management of Hodgkin's disease (206 to 209) It does produce remissions in chronic leukemia and polycythemia, but it is inferior to other forms of therapy.

Miscellaneous.—Bessis (210) reports on the use of replacement transfusion in acute leukemia Of the 38 cases treated, 30 temporary clinical remissions were produced, and 15 had peripheral blood remissions Bierman and associates (124) have observed a striking fall in the white count and regression of the leukemic tissue masses after cross-transfusion studies. They raise the interesting possibility that in leukemia, there may be an inability

may occur in a variety of other disorders, and the marrow must be interpreted in this respect with caution (179).

The modification of the leukemic process in animals and man by chemical and physical agents is of particular interest For a general discussion, the reader should refer to the articles by Karnofsky (180), Reinhard, Good & Martin (181), and Gellhorn & Jones (182). Unfortunately, it may still be said that supportive therapy including transfusions, antibiotics, and psychotherapy are as important in the over-all management of the patients as the agents whose effect is directed specifically at the leukemic tissue. Certain chemotherapeutic agents merit specification discussion.

Folic acid antagonists.—Folic acid and its conjugates were observed by Farber and associates (183) to accelerate the leukemic process Folic acid antagonists were used therefore in the treatment of acute leukemia. *In vitro*, 4-amino-pterylglutamic acid (aminopterin) produces inhibition of mitosis (184). In the nonleukemic marrow of man it produces megaloblasts, hypersegmentation of the granulocytes, and bizarre cells of both leukocytic and erythrocytic series (185) Excessive doses result in aplasia of the marrow. Its effect in destroying lymphoid tissue appears to be in part mediated through the adrenal as shown by Dougherty & Dougherty (186)

Folic acid antagonists have been shown by Law *et al* (187) to inhibit the growth of transplantable acute leukemia in mice. In clinical studies (188 to 192), hematological and/or clinical remissions have been produced in approximately one-third of the cases reported Remissions are considerably more frequent in childhood than in adult leukemia. Both lymphoblastic and myeloblastic leukemia may respond, but monocytic leukemia appears to be unaffected Toxic manifestations are frequent and severe In the gastro-intestinal tract, ulcerations occur with diarrhea, hemorrhage, and intestinal perforation Bone marrow damage may result in generalized purpura and a critical reduction in the functional granulocytes Alopecia occasionally occurs as well as a generalized brownish skin pigmentation These toxic reactions have not responded to large amounts of folic acid. This is not unexpected, since aminopterin appears to be able to compete metabolically with several hundred times its weight of folic acid (193) Folic acid antagonists produce remissions more frequently than occur spontaneously and as many as three or four remissions in one individual. However, in the majority of the patients, survival is not significantly prolonged, and in no instance has the patient been permanently cured Folic acid antagonists in experienced hands have a definite but limited place in the treatment of acute leukemia

Cortisone and ACTH—In view of the action of adrenal oxysteroids in breaking down normal lymphoid tissue, it was logical to try cortisone (compound E) and ACTH in the treatment of lymphoma and leukemia. Experience has shown that while these substances have little effect in chronic leukemia, striking temporary remissions may be produced in acute leukemia In over 100 patients treated, remissions have been produced in about 50

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of the lungs to destroy leukocytes. Miller, Herbut & Jones (211) and Erf, Turner & Miller (212) produce regressions of leukemic infiltrations with extracts from urine and tissues of leukemic patients. These observations are of interest as they provide clues to the nature of the leukemic process

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NUTRITION AND NUTRITIONAL DISEASES[1]

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We begin by expressing our gratitude to our predecessors, Dr. Kahn and Dr. Stare, who wrote the article on nutrition in the *Annual Review of Medicine* for 1950, for they established the principle that in a review of this nature, it would be quite impractical to attempt to cover the enormous field in which so many are forwarding knowledge. Like them, we have confined ourselves to three subjects, our choices being kwashiorkor, medicine in a famine, and the metabolism of ascorbic acid. This is a personal decision determined by our own interests and experience and in no way reflects the importance of these subjects relative to other branches of nutrition.

KWASHIORKOR

Williams (1, 2) published in 1933 and 1935 two papers in which she described a nutritional disease common amongst the children of the Gold Coast Colony in West Africa. The characteristic features of the disease were edema of the hands and feet, profound wasting, a skin which was dry, scaly, and in patches lacking in pigment; the hair was dry, sparse, and often a dull reddish, muddy colour; there was often diarrhea and irritability. At necropsy, a severe fatty degeneration of the liver was constantly found. The disease was most common in children between the ages of one and four years and frequently arose soon after weaning and at the end of a long period of breast-feeding The diet of these toddlers usually contained no milk and a predominance of the cereal, maize (corn). The people of the Gold Coast were familiar with the condition under the vernacular name "Kwashiorkor," which means "the red or brown boy."

Subsequently, this disease has been much studied throughout British Colonial Africa, where it is now known to be widespread. In the last ten years, reports from many parts of the world have shown beyond doubt that Williams was describing a disease not peculiar to any one people, or dependent on a local dietary habit or custom, but a condition that might arise amongst all races of mankind and result from a variety of dietary failures. Many attempts have been made to find a suitable name for this disease in the language of international medicine. "Infantile pellagra," "malignant malnutrition," "polycarencial dystrophy," "nutritional dystrophy," "syndrome dépigmentation-oedème" have all been tried and each has failed to give general satisfaction. Consequent upon this failure of classical nomenclature, we would recommend that the vernacular "kwashiorkor" be officially recognised and given an accepted place in the nomenclature of diseases, alongside

[1] The survey of literature pertinent to this review was terminated in July, 1950.

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TABLE I

DISTRIBUTION OF KWASHIORKOR

	Africa
Gold Coast	Williams (1, 2)
Kenya	Gillan (5)
	Trowell (6)
Uganda	Trowell (7)
	Trowell & Muwazi (8)
Nigeria—Lagos	Hughes (9)
Belgian Congo	Van Daele (10)
	Pieraerts (11)
French East Africa	Bergeret (12)
Union of South Africa—	
Johannesburg	Gillman & Gillman (13, 14)
Durban	Kark (15)
	America
Chile—Santiago	Meneghello, Espinosa & Coronel (16)
Brazil—Rio de Janiero	Carvalho, Schmidt & Pinto (17, 18)
Cuba	Castellano (19)
West Indies	Waterlow (20, 21)
West Indies—Curaçao	Hartz (22)
	Asia
India—Mysore	Ramalingaswami & Patwardhan (23)
Madras	Achar (24)
	Passmore (25)
Indo-China	Passmore (personal observation)
Ceylon	Fernando, Medonza & Rajasuriya (26)
Malaya	Nicholls (27)
Persia	Meiklejohn (personal observation)
	Europe
Hungary—Budapest	Véghelyi, Kemény, Pozsonyi & Sós (28)
Italy	Frontali* (29)

* In 1946, Frontali informed one of us (A P M) that the condition known in classic pediatric literature as "starch dystrophy" was not rare in Italian pediatric practice and that a palpable liver was a common accompaniment This is our ground for quoting him in this context

fundamental lesion in kwashiorkor, *vide infra*) can be produced experimentally in animals by a dietary deficiency either of choline or of substances such as the amino acid methionine, containing labile methyl groups which the body can utilise for choline synthesis. It is tempting to speculate that methionine deficiency is one important factor in the etiology of kwashiorkor. The evidence for protein-deficiency as being the principal factor, although

kala-azar, beriberi, and sprue. As in the case of sprue, the original meaning in the vernacular has been modified and expanded. But language grows and kwashiorkor is now used to describe a well-defined disease.

Although an extensive literature on kwashiorkor exists in a variety of medical journals, yet the disease is rarely described in standard textbooks Indeed, we have recently searched the indexes of some dozen American and British works on general medicine without finding any mention of it. This must be our apology for the following straight-forward and simple account which provides no new fare for the experienced clinical nutritionist.

Distribution—Trowell (3) has recently reviewed the literature and quotes 125 references to the disease in different parts of the world Table I lists a selection of descriptions of nutritional diseases, all of which we believe to be essentially kwashiorkor. A study of these reports should convince anyone that kwashiorkor is no West African tribal disease but a widespread malady affecting many peoples. We, ourselves, have seen kwashiorkor in four continents and in every race of man. It is noteworthy that accounts of the disease have been few in the southern states of the United States of America and in the countries bordering upon the Mediterranean. In these areas pellagra is endemic. Pellagra and kwashiorkor have many features in common, and physicians thoroughly familiar with pellagra (4) are wont to use the diagnosis of this characteristic disease to cover allied conditions, which are indeed clinically and epidemiologically distinct. The distinction between kwashiorkor and pellagra is given in the section on diagnosis.

Etiology—Kwashiorkor occurs under circumstances which include both a breakdown in the food supply and a general failure or absence of hygiene Consequently, the disease may be associated with deficiencies of vitamin A, *thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine,* ascorbic acid, and other vitamins; it is also closely associated both with protozoal diseases, notably malaria and amebic dysentery, and in endemic areas, trypanosomiasis and kala-azar, and with helminth infestation, notably with hook worms and round worms These and other deficiencies and infections frequently contribute to the clinical picture Each may be an important accessory etiologic agent, but none is an essential factor for the appearance of the disease

There is much evidence to suggest that deficiency of protein-rich foods is the primary cause of the disease On the epidemiologic side, kwashiorkor occurs most frequently at that period of life when the active growing child has additional needs for protein, and among populations in which milk and other animal proteins are luxuries—for the most part *unavailable to the* children of the poor. It is also most commonly (but not invariably) found in peoples whose staple food is either maize or else one of the tropical roots such as cassava or manioca. The proteins of maize are known to be of low biologic value, and the tropical roots for the most part provide a lower proportion of calories as protein than do cereals On the experimental side, there is the demonstration that the accumulation of fat in the liver (perhaps the most

in areas where kwashiorkor is endemic is by no means a rarity, but whether it is also a true sequela is a matter for speculation and further study.

In severe cases, this liver damage is associated with a low level of serum proteins and particularly of serum albumin, which is commonly below 2 0 gm. per 100 ml. [Trowell (3)]. Under these conditions, there is edema, susceptibility to infections, and a poor prognosis The importance of lesser degrees of liver damage found in the subclinical cases is uncertain. Davies (31) has put forward the hypothesis that the partially-damaged liver cannot dispose of the small amounts of female sex hormone normally produced by the male He postulates that the male population of the whole continent of Africa is partially feminized owing to this widespread liver failure; in evidence, he adduces the frequency of gynecomastia and testicular atrophy in Africans The psychologic, social, and even political implications of this hypothesis are, of course, immense. It is certainly an ingenious idea.

The pancreas.—Recent studies by Davies (30), Hartz (22), and Véghelyi *et al.* (28) have each indicated that the lesions in the liver are preceded by lesions in the pancreas. The earliest histologic changes are fragmentation of the pancreatic parenchyma and cyst-like dilatation of the acini Then follows a diffuse peri-acinar and peri-lobular fibrosis. These writers suggest that, essentially, kwashiorkor may be a pancreatic disorder due to malnutrition, and that the liver changes are secondary

These observations may explain an old error amongst army doctors new to the tropics In the last war not a few healthy Indian and African soldiers found themselves in army hospitals—labelled mumps Indians and Africans often have large parotid glands giving their faces a slightly swollen appearance, not unlike mumps. This slight facial swelling may well be due to an old-standing mild degenerative process in the parotid gland, acquired in childhood at the same time as a similar degeneration of the pancreas, each primarily nutritional in origin and each now healed with little or no disability.

The small intestine.—An important lesion is an atrophy of the whole intestines [Passmore (25)]. All coats, mucosa and submucosa, are involved The small intestine is most affected, becoming progressively thinner from the duodenum down to the ileo-cecal junction. Indeed, the last two feet may be so thin and transparent as to resemble the texture of tissue paper. The mucous membrane of the small intestine is smooth and atrophic, and clearly its digestive and absorptive functions must be seriously impaired. This change was a striking feature of a group of monkeys who were fed on a poor rice diet and developed a condition closely resembling, if not identical with, kwashiorkor [Radhakrishna Rao (32)] In sections of the intestines of these animals, degeneration of the intrinsic nerve supply was an early and characteristic feature. Whether this intestinal degeneration and consequent failure of function is a primary or secondary feature of the pathology of the disease is uncertain. That it plays a big part in the clinical progress of severe cases is beyond doubt

Clinical description—A nutritional disorder which affects the liver must

not altogether conclusive, is sufficient to justify the use of protein-rich foods as the principal therapeutic agents It also indicates the need for public health and agricultural measures to increase the protein supply of affected communities and especially to distribute protein-rich foods to children, via welfare services.

On the social side, it is important to stress the factor of parental neglect. This is sometimes unavoidable, as in the case of many of the children first described by Williams, whose mothers had recently died In most parts of the tropics, the neglect is due to that wretched vicious circle of poverty and ignorance that is such a stumbling block to health The sporadic cases that are occasionally seen in hospitals of industrial cities outside the tropics are usually children from broken homes, and here the neglect is criminal.[2]

Pathology.—Detailed studies have been made in Uganda by Davies (30) and in Johannesburg by Gillman & Gillman (13).

The liver.—These investigators have described the changes found in the liver, both in specimens obtained by biopsy and at necropsy. The liver changes are certainly the most striking and perhaps the most fundamental feature of the pathology of kwashiorkor. In early lesions there is an accumulation of small droplets of fat within the liver cells at the periphery of the lobule. As the disease progresses the droplets expand and extend. In fatal cases all the liver cells may be filled each with a large fat droplet, pushing aside the cell nucleus and reducing the cell cytoplasm to a narrow rim As the Gillmans point out, some of their photomicrographs of liver sections could readily be mistaken for sections of perirenal fat. In advanced cases there is an infiltration by round cells and a fine fibrosis surrounding the periphery of the lobules. *This may finally progress to a severe cirrhosis.*

Studies of the liver histology have now led to a much better understanding of the natural history of kwashiorkor In some parts of Africa it is hard to find a single child with an histologically normal liver. Even though superficially the child may appear well, the liver will show some degree of fatty degeneration Should there be a sharp or sudden deterioration in the diet, this will lead to a severe fatty degeneration and the full clinical picture of kwashiorkor In these advanced cases, liver damage is so severe that recovery is impossible; this led Trowell to suggest the name "malignant malnutrition." Far more frequently the disease continues for many years without overt symptoms; the fat is gradually absorbed and the fibrosis extends, so that the child enters adult life with a mild fibrosis of the liver Cirrhosis of the liver in many countries in the tropics is common and probably attributable to this process The familiar picture of ascites in the medical wards of tropical hospitals may often be the final result of a long period of malnutrition in infancy and early childhood Primary cancer of the liver

[2] Since this review was written, an intriguing alternative explanation of the etiology of kwashiorkor has been proposed (101), apparently, it is a simple matter of possession by devils

of anemia in relation to kwashiorkor and tropical parasites is given by Lehmann (34).

Coincident infections are characteristic of the disease; in 37 cases studied by Trowell (3) in Uganda, these were· malaria 31, hookworm 25, ascaris 6, tenia 2, rhinitis 28, bronchitis 12, pneumonia 8, bacillary dysentery 4, amebic dysentery 3, congenital syphilis 3, pulmonary tuberculosis 2. Such is a typical list.

Lesions attributable to riboflavin deficiency (angular stomatitis, cheilosis, oro-genital syndrome, and interstitial keratitis) and to vitamin A deficiency (xerophthalmia, Bitôt's spots) are frequently associated with kwashiorkor, but are not essential features.

Diagnosis —The first essential for diagnosis is a history of many weeks subsistence on a diet defective both in quantity and quality and especially lacking in animal proteins If, with this history, there is marasmus, edema, enlargement of the liver, crazy-pavement dermatosis, and the typical hair, then there can be no doubt as to the nature of the disease. There is no differential diagnosis from the chronic infectious diseases as these are part of the condition, and the presence of one or more such infections is to be expected.

The distinction from pellagra is important. In pellagra, the skin lesions are photo-sensitive and confined to the exposed surfaces; pellagra has a well-marked seasonal incidence and is less common in winter months. In stable communities, kwashiorkor is essentially a primary disease of children, whereas pellagra is most common in adults. Pellagrous dementia is not seen in kwashiorkor

Treatment —There are two principles The first is to see that the patient eats a good mixed diet containing plenty of milk or other sources of animal protein. The second is to seek out all parasites and infections and eradicate them

Available foodstuffs and prevalent infections vary so much in different countries that it is unprofitable to discuss details. As regards dietary therapy, a good cook in the kitchen and an enthusiastic nurse in the ward are more important than regimens and schedules Patients usually have poor appetites and must be coaxed to eat with appetising food attractively served. Once the appetite has returned, recovery may confidently be expected In kwashiorkor, many infections, notably malaria and amebiasis, lie dormant and present no overt evidence of their presence Yet such latent infections will impede all nutritional therapy Great diligence, skill, and knowledge is needed to find out and remove all of these local diseases.

Many observers have reported that children have become rapidly worse when treated with concentrated preparations of vitamins. The distribution of vitamins in the body appears to be finely balanced and an overloading of one may exaggerate the effects of deficiency of another We would endorse the statement of Trowell (3):

It must be stated with the greatest clearness that all vitamins are forbidden, so

present itself in many forms. It is probable that for every overt, clinically distinct case, there are numerous persons with mild nonspecific signs and symptoms. In districts where the disease is endemic, failure to grow or loss of weight, diminished energy and vitality, impaired powers of concentration, and increased susceptibility to infections may all be early evidence of the disease At present, an early diagnosis can only be made with certainty by liver biopsy Kwashiorkor may occur at any age, but in its characteristic and florid form, it is most frequently seen in children between the ages of one and four.

Such children are below normal standards of development for their age They are often severely wasted and lacking in both subcutaneous fat and muscle. They may be unable to support themselves. Edema may be widespread, but affects especially the limbs. The liver can usually be palpated with ease and may reach down to the umbilicus. The skin is dry, rough, and scaly. In severe cases, a "crazy-pavement" dermatosis is characteristically seen. The name provides an excellent description. Irregular cracks occur all over a dry hard epidermis which are superficial and are usually 2 or 3 mm apart, but quite irregular in pattern. Deeper cracks sometimes occur at wider intervals and these may be infected and ulcerated. Dead layers of the superficial squamous epithelium flake easily These changes may be universal, but are most marked on extensor surfaces and points of irritation and pressure. The face is seldom affected. The lesions are not photosensitive. Irregularly distributed pigmentation is characteristic, with areas of hypo-pigmentation which particularly affect the face and may be symmetrical Secondary infection of the skin is common The hair is sparse, dry, and may be discoloured A variety of failures of hair pigment occur, and the hair may appear brown, red, or grey, most commonly it looks ugly and muddish. These changes are, of course, most conspicuous in negroes whose hair in health has a fine glossy appearance

Loss of appetite is a prominent and early feature which may seriously impede treatment. Flatulence and abdominal discomfort are common, and in severe cases there is diarrhea. This is not inflammatory and occurs without evidence of dysentery The stools are usually watery, fecal in colour, and often contain visible particles of food completely undigested Microscopically, undigested starch grains and vegetable fibres can easily be seen. If the diet contains fat, this is passed undigested The nature of the diarrhea is such that it would appear to be the result of a small-intestinal hurry with failure of both digestion and absorption. Radiological examination of the large bowel shows a characteristic picture [Scott Brown & Trowell (33)].

Kwashiorkor is associated with some degree of anemia If this is severe, there is almost invariably heavy infection either with malaria or hookworm But characteristically, the anemia is moderate (hemoglobin levels 7 to 11 gm. per 100 ml.) and usually normocytic in character. This probably reflects a general protein deficiency, and it improves *pari passu* with the general condition, with dietary therapy, and with specific treatment. A full discussion

social, economic, and political factors that poise the delicate balance between the outflow of manufactured goods and of services to the countryside in return for a supply of food are uncertain and may readily be upset. Then, hunger and perhaps famine must follow. It is, unfortunately, all too probable that many young doctors and students in medical schools throughout the world to-day will, at some time in their careers, be called upon to carry out their professional duties under famine conditions So we have thought it profitable to put together a few generalisations that have arisen out of our experiences in the last 10 years These are based in part on personal experience, on the literature already cited, and also to a great extent on conversation with those who have lived and worked in famines. We do not attempt the impossible task of summarising past literature, but try to rough out a few principles which we hope may be found useful in the difficult times which may come. First the primary causes of famine must be set out briefly. They are four in number.

Widespread failure of crops due to lack of water.—Many millions of people in tropical and subtropical countries have lived since the beginning of history under this threat. Vast numbers have died in famines arising from drought. Irrigation schemes have enabled man to preserve and, in a relatively small way, control the rain after it has fallen Thanks to the hydraulic engineers, millions of acres of land are now partially independent of direct rainfalls Yet there are no signs that science in the near future will be able to insure a regular rainfall over all the cultivated areas of the world In many districts, people must continue to live under the threat of a failure of the rains, and famine conditions from this cause will continue to arise

War and civil disturbance—The inhabitants of Europe, North America, and most other temperate regions enjoy such a regular rainfall that natural famines caused by catastrophic failures of the crops from lack of water are unknown European famines have been characteristically man-made and have arisen as a direct result of human error or wickedness War is a potent cause. Armies living on and fighting over a countryside may cause famine by destruction or looting of crops, peasants may be enlisted into their ranks in such large numbers that the man-power for the effective cultivation of the fields is no longer available In these ways, many famines arose in Europe, especially in the religious wars of the sixteenth and seventeenth centuries In the twentieth century, the effects of fighting on the countryside in Europe have been seldom so widespread or prolonged as to cause major destruction of the crops except in relatively local areas Famine conditions have arisen in the great industrial cities more frequently than in the countrysides The disruption of large transport systems and the economic structure of society necessary for the feeding of urban populations has in many cases led to famine (e g., in Vienna in 1919). Finally, we have had the disgraceful spectacle of the deliberate production of famine conditions for the purpose of exterminating large masses of people deemed to be undesirable. This has happened in the ghettos of Warsaw in 1942, in other cities, and in the various camps in

are unnatural foods like dehydrated liver, desiccated stomach, proteolysed meats, casein hydrolysates These all distract time and money and attention Everything must be directed to overcoming the false economy which would deprive wards of essential diets, but would flood them with expensive vitamins and quack foods All the time one must have in mind the parsimony of food votes, the conservatism of the kitchen, theft, maternal inertia and neglect by nurses

When cirrhosis of the liver has developed, the outlook is poor and treatment of limited value In these respects the condition is similar to other types of cirrhosis of the liver

Prevention.—As already stated, poverty and ignorance are two fundamental causes of kwashiorkor. Medical men are seldom able to attack directly the former, but we can do much to defeat the latter. In all countries where kwashiorkor is prevalent, there is an appalling ignorance of mothercraft. This can only be overcome by the development of effective maternity and child welfare services. The setting up and extending of such services must be the main preventive measure against kwashiorkor. In this educational work, it is most important to study the mind and habits of the local mothers and to remember that plans and schemes that have been proved admirable in Edinburgh or Baltimore may fail in Timbuctoo

MEDICINE IN A FAMINE

The history of human endeavour has been interrupted by irregular but not infrequent accounts of times when starvation was common and devastating famines occurred in which many millions of people perished. The story goes far back. All of us are familiar with the tale told by an old Hebrew writer (35) of how a young Jewish administrator named Joseph advised the Pharoahs on famine relief measures in ancient Egypt Thereafter, a long list of famine literature links up with accounts of recent disasters In the decade 1940–1950, there has been famine in the ghettos of Warsaw (36), in civilian internment camps in central Europe (37, 38), in Holland (39) and Greece (40), in besieged Leningrad (41), and in prisoners-of-war camps in eastern Germany (42) In the Far East, many of the inhabitants of civilian internment camps run by the Japanese lived under famine conditions (43, 44), so also did the prisoners working on the Burma-Siam railway (45) and some of the peoples of the Netherlands East Indies (46) during the Japanese occupation of those islands A major famine occurred in Bengal (47). There has, in addition, been a great laboratory study of the physiologic and psychologic effects of a period of several months of partial starvation upon a group of human volunteers (48, 49). Also the story of the Irish famines of 1845 to 48, perhaps one of the most massive of human tragedies, has recently been brilliantly retold (50)

Only a blind optimist can think that this tale is now complete Over half the population of the world are simple peasants struggling to produce a sufficiency of food for themselves and their families and subject to all the uncertainties of primitive agriculture In the great industrial centres, the

social, economic, and political factors that poise the delicate balance between the outflow of manufactured goods and of services to the countryside in return for a supply of food are uncertain and may readily be upset. Then, hunger and perhaps famine must follow. It is, unfortunately, all too probable that many young doctors and students in medical schools throughout the world to-day will, at some time in their careers, be called upon to carry out their professional duties under famine conditions So we have thought it profitable to put together a few generalisations that have arisen out of our experiences in the last 10 years These are based in part on personal experience, on the literature already cited, and also to a great extent on conversation with those who have lived and worked in famines We do not attempt the impossible task of summarising past literature, but try to rough out a few principles which we hope may be found useful in the difficult times which may come. First the primary causes of famine must be set out briefly They are four in number.

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which Nazis rounded up those millions of unfortunates who had no place in their society.

Destruction of the crops by diseases and pests.—The great Irish famines of the nineteenth century were caused by the destruction of the potato crops by the blight, a fungus infection of the plant. Two to three million persons died in these famines, and large numbers emigrated. The responsible fungus had a profound effect on both European and American history. Wherever one single crop dominates agriculture, there a risk always remains that the crop may perish from a plant disease, either new or old. In those large areas of the world liable to plagues of locusts, safety from famine can only be purchased by constant vigilance and fighting against these greedy and prolific insects.

Great natural disturbances.—Earthquakes and floods are a constant threat in many parts of the world These are catastrophic in their action, but usually only short in duration Great destruction of crops, food stores, and communications may result. The threat of famine is common, but can usually be overcome, if relief measures organised in neighbouring undamaged districts are effectively introduced Thus, following the great Ecuador earthquake in 1949, over 50,000 children received food and other relief through the United Nations International Children's Emergency Fund (51).

The Effects of Famine

These are numerous and diverse, but three stand out and overshadow all others in their importance They are (*a*) deaths from starvation, (*b*) panic and moral disruption leading to widespread chaotic and uncontrolled population movements, and (*c*) the outbreak and spread of major epidemics It is of the utmost importance in a famine that all working in medical and other relief agencies keep these in their right perspective, that is foremost in the mind. In a famine, a vast variety of problems of great appeal both to heart and mind arise and demand action But charitable emotions and scientific interests must be disciplined, time and energy, and stores and equipment, which could profitably be used to prevent or mitigate the three great tragic events of famine, must not be allowed to be diverted to lesser causes

The Prevention of Deaths from Starvation

The problem of the minimum amount of food necessary to preserve life in times of shortages has long been debated In 1946, the Food and Agriculture Organisation (FAO) of the United Nations set out recommendations for subsistence and maintenance levels of calorie intake (52). These are shown in Table II. We agree that these figures represent a practical compromise in an emergency between physiological needs and difficulties of supply. It is the first duty of the medical profession to convince those in administrative charge of a famine that, unless food at the level of the Emergency Subsistence scale is provided, deaths resulting directly from starvation may occur and civil unrest is probable. Unless food is supplied at the level of the Tem-

porary Maintenance scale, working efficiency will be low, and deterioration of health and undernutrition will probably result. In putting these points before a particular authority, an individual doctor must make it clear that he is not voicing an individual opinion, but giving a judgment based on the combined experiences of a great many medical men and physiologists, obtained under a variety of famine conditions.

TABLE II

CALORIE INTAKE

Category	Subsistence and Maintenance Levels: Emergency Subsistence Level*	Temporary Maintenance Level†
0 to 2 years	1,000	1,000
3 to 5 years	1,250	1,500
6 to 9 years	1,500	1,750
10 to 17 years	2,000	2,500
Pregnant and nursing women	2,000	2,500
Normal consumers (sedentary)		
Male	1,900	2,200
Female	1,600	1,800
Moderate workers	2,000	2,500
Heavy workers	2,500	3,000
Very heavy workers	3,000	3,500

* *Emergency Subsistence level* needed to prevent the most serious undernutrition leading to disease and the danger of civil unrest

† *Temporary Maintenance level* sufficiently high to maintain populations in fairly good health but not sufficient for rapid and complete recovery.

The second task is to assist in the drawing up of a system of distribution or rationing For this, a knowledge of the age and sex composition of the population is necessary If mass movements are taking place, this will be very difficult; yet every effort must be made to obtain and keep up-to-date records both of the numbers and of the nature of the people to be fed In separating the adult working population into the four groups, if effective and efficient work is necessary, then there must be a liberal interpretation of what constitutes "heavy" and "very heavy" work There is then the task of translating the figures for individual daily calorie requirements into amounts of available foodstuff per week and per head In practice, during a famine the number of foodstuffs available in sufficient quantity for distribution, which can appreciably influence calorie intake, is small It is of the utmost importance to see that these are equitably distributed as far as possible according to the scales in Table II. This table gives a statement of requirements of calories needed in individual stomachs It cannot be equated exactly with a

corresponding amount of food stamped on a ration card. Inevitable losses and wastage must occur. How great these are must depend in part on the general efficiency of the administration, the extent of corruption amongst the general population, and the size and nature of the black markets In assessing these, much local knowledge and shrewd judgment are necessary. It is highly desirable to have some survey organisation to check up how much food people are actually eating and to compare this with how much is supposed to be available. An admirable account of such a survey organisation at work in Vienna in the second half of 1945 has been given (53). Black markets can only flourish and become a danger to health if too elaborate a system of distribution is introduced which the administration has not the strength to control. If the administrative control is limited to those few foods that are of high calorific value and are available in relatively large amounts, and this control is effective, then the administration will have done its utmost to prevent that first disaster of famine, deaths from starvation. It is an error to attempt too elaborate a system of rationing which it is impossible to enforce.

Milk.—The need for calories, for food, is the overwhelming consideration for hungry people, yet there are three subsidiary factors which should be stressed. First, there is the special position of milk, which is very valuable as an easily assimilable source, both of animal protein and of calcium, and thus, is of the utmost importance for growing children and seriously ill patients in hospitals. Under famine conditions, indigenous sources of supply are always inadequate (dairy cows dry up or go to the butcher before men get really hungry), and supplies imported by relief organisations are inevitably limited So precious is milk for health that under certain conditions it may be expedient to consider it as a medicine rather than as a food In such a circumstance, all milk under the government control should be handed over, not to shops and dairymen, but to medical stores Thence it would be distributed through maternity and child welfare services, schools, and hospitals to those who had the greatest need. It is obvious that in a general review, such a point cannot be elaborated in detail Suffice it to repeat that milk is so important amongst a starving people that often it may best be considered as a medicine If the medical profession can drive home this point to the administrative authorities, they will be able to get the greatest measure of control of milk distribution.

Vitamins—Large outbreaks of deficiency diseases have not been a general feature of recent famines. Under most circumstances, men die of starvation from lack of calories before there are any obvious signs of vitamin lack In most famines, vitamin tablets and concentrates should be low in the order [illegible] es of general amelioration of [illegible] vitamins. Two exceptions [illegible] people with any access to gardens or green fields will not die of scurvy, in famines in industrial cities and in desert and semi-desert districts where no blade of green is visible, scurvy may break out and kill quickly In an industrial city, no great dif-

ficulty should be experienced in providing synthetic ascorbic acid. It is easily synthesised and distribution does not involve the transport of large masses of material; sufficient supplies for a large city could easily be dropped by air. Among a scattered rural people in an arid land, it is possible to manufacture Vitamin C by sprouting pulses such as peas or beans. A simple recipe is as follows (54):

> A sufficient quantity of whole (unsplit) pulse, dal or gram (say 1½ to 2 ozs per man) is soaked in water for 12 to 24 hours A container big enough and holding sufficient water to allow for expansion should be used Then pour off the water, remove the grains and spread on a damp blanket in a layer thin enough to allow access of air and cover with a blanket. Keep the blankets damp by sprinkling with water. In a few hours, shoots will appear, and when these are ½ to 1 inch long the process is complete. Vitamin C content is maximum after about 30 hours of germination.

This simple procedure has saved many lives.

When the principal source of calories is machine-milled polished rice or other highly refined cereal, beriberi is liable to break out. This can only be prevented, in the absence of an all-round dietary improvement, by vitamin concentrates. If either wheat or rice-bran should be available, dried preparations or aqueous extracts are rich sources of vitamins and excellent preventatives. Unfortunately, yeasts grown on a poor medium, which is all that may be available in famine camps, do not always synthesize the B group of vitamins in sufficient quantities and, in practice, may prove of limited value as a prophylactic (43). It is important to remember that the risk of beriberi occurs when supplies of refined cereal are suddenly increased without a corresponding rise in intake of other foods A sudden increase in the ration may precipitate an attack of beriberi

Psychological considerations.—Any departure from the usual dietary pattern of a people will profoundly affect their morale It is clearly advisable in a famine to provide foods to which the people are accustomed Thus habitual rice-eaters, if supplied with only wheat or millet, will be greatly upset. They will not have the knowledge of how to prepare the strange foods, and may lack essential culinary equipment Under other circumstances, it has been claimed that persons habituated to a central European diet must have certain quantities of fat and animal protein without which they could not exist, even though still receiving the amounts claimed as absolutely essential for life. These amounts, in Europe, are often greater than the normal quantities eaten by Oriental peoples which, for them, are fully sufficient for health. It is clearly advisable to consider as far as possible local customs and taste in any time of shortage, but if there is real danger of deaths from starvation then every effort must be concentrated on providing foods with sufficient calories.

The Prevention of Panic, Disruption of Morale, and Widespread, Chaotic Movements of Population

Perhaps the greatest tragedy of famine is the widespread and often aimless migrations in which families are completely disrupted and children ir-

retrievably separated from their parents. Such social lesions take at least a generation to heal. Modern medicine can play a great rôle in maintaining morale amongst a hungry and dispirited people. Medical relief provides a focus of order and sanity in the midst of utter confusion. It can be a symbol of hope, and keep the people together. If medical relief is to be fully effective in this manner, it must be widely dispersed throughout a famine area. Both trained personnel and equipment are inevitably limited; they are best used in small hospitals and dispensaries, each as close as possible to a small population centre. Large hospitals away from many of the people are a waste of valuable material. In a famine it is usually quite uneconomical to provide heavy equipment for refinements in diagnosis and treatment. Every effort should be concentrated in getting simple drugs and remedies freely available Healthy and intelligent persons, even if hitherto quite ignorant of medical matters, can often be rapidly trained to act as orderlies and nurses. At Belsen, one of us (A.P.M.) found that medical students made excellent workers; their energy, enthusiasm and common sense more than compensated for any deficiencies in technical training. A big responsibility inevitably falls on all medical men in a famine for organising a subordinate medical staff. The improvisation and the collection of simple medical equipment and hospital furniture is also his duty. Indeed, every famine doctor must be first and foremost an administrator It is his task to see that many people in need get some medical care, and the clinical interest or human appeal of individual cases should not distract either his time or skill from that task.

Famine hospitals are inevitably overcrowded, and feeding arrangements must be simple There is no place for elaborate dietary regimes The first essential is the provision of simple meals, as far as possible attractively cooked and served. The provision of suitable kitchen and dining-room accommodation may be a difficult problem and, if so, must command the doctor's attention Severely undernourished persons often have lost their appetite and have to be coaxed to eat A large and diverse stock of flavouring

bad and many deaths from starvation are occurring, judgment is required in picking out early those who can be saved by special care and attention Too much time of the nursing staff must not be spent on hopeless and desperate patients, if this means the neglect of those who could be saved by more timely care.

Experience has shown how much even a small medical service, if properly utilised, can do to maintain the public confidence. In such a service, individual doctors inevitably must be administrators first, and the chief tasks must be the organisation and supervision of a large subordinate staff and the provision of this staff with a sufficiency of simple remedies and equipment. The successful famine doctor is always a master of improvisation.

The Prevention of Epidemics

The most devasting diseases liable to arise are louse-born typhus in temperate zones and cholera in tropical regions. Smallpox and influenza are close followers, and, in those countries where conditions are suitable for insect transmission, malaria is intimately associated with famine (55). But under conditions of social stress, any infectious disease endemic in a population may assume epidemic proportions For instance, recent experience has shown that tuberculosis increases greatly and may assume epidemic proportions in famine. It often assumes unusual forms, and sometimes is without obvious symptoms. Health authorities must prepare for possible epidemics of all indigenous infections, and also for the importation of new diseases with the influx of refugees and migrants from neighbouring districts and countries. We have named five diseases, not because they are necessarily the most likely to arise in any particular future famine, but because of their dominating role in the past. It is important to realise that it is not starvation per se that gives rise to greatly increased individual susceptibility to these diseases, but rather the social disruption that breaks down the hygienic environment and leads to conditions ideal for transmission of disease. There is an abundance of clinical experience to show that these diseases strike alike, if circumstances permit, both the well-fed and the starved Further, the mortality rates among infected persons are seldom markedly higher in famine than in normal circumstances. We would not state categorically that individual susceptibility and resistance to infections is not lowered in famines, but such changes are slight in comparison with the increased risks of exposure; hence, the paramount importance of striving to maintain as far as possible good levels of hygiene in a famine. It will be noted that of the five infectious diseases already named, all except influenza can be prevented and controlled by hygienic measures which are well understood in theory and not difficult to apply in practice in a stable and healthy society

From these considerations, it follows that a paramount duty of a medical authority in an area in which famine conditions may be anticipated or have already broken out is to forecast all the epidemics that could conceivably arise, and then to collect a central depot of stores and trained personnel capable of dealing at once with any outbreak that may arise. Preparations must also include a widespread, quick, and efficient diagnostic service It is usually technically easy to stamp out a single isolated focus of infection. But once subsidiary centres of spread have been established, an epidemic will gather momentum like a snowball. Then, perhaps the most elaborate and expensive measures may fail to control the disease A simple and speedy method of notification of any new disease to the medical administrative centre from persons at the periphery of the famine is necessary. Notification and hygienic action must follow at once upon clinical suspicion Delays for laboratory confirmation of the diagnosis of such diseases as typhus, cholera, and smallpox must never be an excuse for inaction. The necessity for a quick and effective

diagnostic service is another powerful argument for the dispersal of medical and sanitary personnel in a famine. A nurse or medical orderly in an isolated clinic or dispensary may be able to give notice of the appearance of a new disease several hours or even days before patients begin to appear at main medical centres

Medical authorities in a famine must impress upon the general administration the necessity of maintaining general standards of hygiene and public health. Normal health services are inevitably strained, often far beyond capacity. The administration must be made to see the importance of giving a high priority to the hygiene services in money, basic materials, and labour

The Work of the United Nations Relief and Rehabilitation Administration (UNRRA)[3]

After a discussion of the three major aims of famine relief, it is pertinent to summarise the work of UNRRA in the prevention of famine in Europe in 1945, 1946, and 1947 and to indicate the scale of the measures used. When the tide of war began to turn, plans for bringing immediate relief to the invaded countries awaiting liberation were pursued with vigor and imagination by the United Nations As early as November, 1943, representatives of 44 nations met in the White House at the invitation of President Roosevelt. There, they brought UNRRA into being. a unique organisation for international relief on a grand scale. The countries that had not been invaded agreed to contribute 2 per cent of their income to the resources of UNRRA. The largest contributions were from the United States, 2 7 billion dollars, from Great Britain, 625 million, and from Canada, 139 million. With these vast resources—three times more than was spent on relief after World War I—UNRRA poured vital supplies into Albania, Austria, Byelorussia, China, Czechoslovakia, Italy, Greece, Poland, the Ukraine, and Yugoslavia Limited aid was also given to seven other countries In the three years of its operation, beginning in March, 1945, 25 million tons of goods costing three billion dollars were transported overseas by UNRRA in more than 6,000 ships Other goods were purchased on the spot from Army supplies and other sources and turned over for relief purposes This huge volume of essential goods included locomotives, trucks, and freight cars necessary for the transport of food to centres of population, more than 300,000 farm animals, thousands of tractors and ploughs, and many tons of seed grains necessary for the restarting of agriculture in devastated areas, besides the fully equipped hospitals, much needed medical supplies, and personnel necessary for the health and life of the invaded countries But agriculture could not be set on its feet overnight and, in the meantime, the people had to be fed, the most vital part of UNRRA's work was, therefore, the provision of food, foodstuffs of every kind including hundreds of tons of dried milk for children, but chiefly, bread grains In all, UNRRA shipped enough grain to make about 12 billion one-

[3] The following brief account is based on the personal knowledge of one of us (A.P.M.) acquired during three years work with UNRRA

pound loaves, enough to give five such loaves to every man, woman and child in the world The result was that at least three famines that might have involved 15 million people in Europe were prevented; untold misery, hardship and underfeeding among many more millions were alleviated.

It was a condition of UNRRA aid that the supplies sent in should be distributed without regard to politics, race, or religion. In this latter day (1950) of conflicting ideologies and international tensions, it is a pleasure to recall that this condition was effectively observed. In conclusion, we are not so naive as to think it possible to collect and condense into nine or ten pages of a review all recent experience of famine. Here only some of the most striking and comprehensive accounts have been listed, and the headlines of those points, which in our opinion are likely to prove important in the future, set out. We hope that these may stimulate reflection and discussion now, for there can be little doubt that some of our readers will in the future find themselves suddenly loaded with great responsibility in the hurly-burly of a famine.

METABOLISM OF ASCORBIC ACID

We have chosen this topic for review partly because of its current interest in relation to the suprarenal cortex, but also for the personal reason that our interests in nutrition arose twenty years ago when we were students of R A. Peters at Oxford. He introduced, then, the concept of a "biochemical lesion" and was the first to show, unequivocally, that a vitamin (thiamine) had a specific enzymic action *in vitro* (56) The enzymic behaviour of other vitamins, notably riboflavin and nicotinic acid, has since been elucidated, but the nature of the biochemical lesion in ascorbic acid deficiency is still elusive. It is of interest to ourselves and, we hope, to others, to consider how far the present evidence goes in explaining the biochemical behaviour of ascorbic acid in human health and disease

Previous reviews—The reviews which originally had appeared in the *Journal of the American Medical Association* in 1938[4] by King (physiology), Dalldorf (pathology) and Smith (requirements), provided excellent summaries of existing knowledge of the vitamin up to that time Later two useful reviews, from the clinical standpoint, were provided by Ralli & Sherry (58) and Pijoan & Lozner (59) Since then, so far as we know, there has been no attempt at a fresh assessment of the literature, nor did there seem any need for it, until the great discovery at the Mayo Clinic of the astonishing clinical effects of cortisone awakened general interest in the suprarenal cortex and revived the question, why is ascorbic acid concentrated in that gland?

Chemistry—It will be remembered that it was from the suprarenal gland that Szent-Gyorgyi first isolated the vitamin as "hexuronic acid" in 1928. This acid was identified with vitamin C by King and subsequently synthesised almost simultaneously in the laboratories of Reichstein and Haworth

Pathology—The morbid anatomy of ascorbic acid deficiency has been

[4] Subsequently published in book form (57)

greatly assisted by studies on the guinea pig, the only animal other than man and the primates known to be subject to scurvy. Wolbach and his colleagues (60) at Harvard provided the first clear picture of the morbid histology of scurvy; they demonstrated the loss of collagen from connective tissue and of intercellular cement and the defective formation of dentine and of osteoid tissue in bone. Up to the present, this is the one absolutely certain characteristic bodily change that is known to result from ascorbic acid deficiency.

The histologic changes in the suprarenal glands of scorbutic guinea pigs were first described by a distinguished Irishman, McCarrison (61), in 1921 His observations were confirmed and extended by Randoin (62) and by Bessey *et al* (63). The chief change is a loss of fat and cholesterol from the cortex. The histologic identification of ascorbic acid in the cells of the cortex was made by an Australian, Bourne (64), using his silver nitrate method

Human scurvy.—The first good clinical account of scurvy in the English language was written by Lind who was a graduate of Edinburgh University His classic, *A Treatise of the Scurvy* (65), was published in Edinburgh in 1753 Another Edinburgh-trained physician, Stark (66), experimentally induced scurvy in himself, having been encouraged thereto by the stimulating conversation of Benjamin Franklin Unfortunately, he developed a secondary infection from which he died in 1770, in his thirtieth year. This dangerous experiment was not repeated until a young American surgeon, Crandon (67), successfully induced scurvy in himself in 1940. To this single splendidly-conducted experiment we owe a large part of our present understanding of the biochemical and histologic changes in human scurvy. This experiment has lately been repeated in Britain on 13 volunteers, with seven others serving as controls (68), Crandon's observations were confirmed and extended

Distribution of ascorbic acid in the body—The human body, when fully saturated with the vitamin, probably holds a total of 4 to 5 gm. [Crandon *et al* (67) Lowry *et al* (69)] The vitamin is normally present in the blood plasma and, under conditions of full saturation, reaches a level of 1 0 to 1 4 mg. per 100 ml The latter figure may be regarded as a kind of "renal threshold" [Van Eekelen (70), Faulkner & Taylor, (71), Ralli *et al* (72)]; attempts to produce higher blood levels than this by means of massive oral doses merely result in rapid loss of the excess vitamin in the urine Small amounts of the vitamin are still excreted when the plasma level is much lower

No normal person in Britain is ever fully saturated with ascorbic acid unless constantly dosing himself with the synthetic vitamin or eating far more fruit and vegetables than his neighbour, in which case he ceases to be normal A state of full saturation is common only among people with food habits very different from ours Our traditional diet is certainly not exciting, but we seem to do quite well on it. There is no evidence that saturation is necessary for "positive health "

The measurement of ascorbic acid in serum or plasma has only one diagnostic use: in patients suspected of scurvy. If any measurable amount of the

vitamin is found, the case is not one of scurvy. In human subjects deprived of ascorbic acid, the vitamin disappears from the plasma many weeks before signs of scurvy appear (67, 68). A better index of the degree of saturation of the body tissues is provided by determining the ascorbic acid content of white blood cells and platelets by the method of Butler & Cushman (73). Normally, this amounts to 20 to 40 mg. per 100 gm. and falls to low levels only with severe depletion (67, 68, 69).

Ascorbic acid is not uniformly distributed throughout the human body. Apart from the suprarenal cortex, from which it was first isolated, it has been found in the adult (74) to be concentrated in the pituitary body, corpus luteum, brain, pancreas, liver, and spleen. It is presumably in these organs that it exerts its chief metabolic activity, whatever that may be In the course of this activity, some of it disappears

Normal rate of catabolism of ascorbic acid—It should be possible to measure the rate at which a normal individual uses up the vitamin by determining the dietary intake necessary to maintain a constant level in plasma, white blood cells, and urine In fact, the rate at which it is catabolised appears to depend very much on the degree of saturation of the body and the amount therefore available to the tissues This was pointed out by Van Eekelen (70) in 1936 Ralli and her associates (72), in a detailed study of three normal individuals fully saturated with the vitamin, found that about 90 mg were catabolised daily, no large excess appeared in the urine until the daily intake exceeded 100 mg Yet seven persons in another experiment (68) kept fit on a total daily intake of 10 mg for over five months (three of them for nine months) Moreover, in six individuals in whom scurvy was experimentally induced, a daily dose of merely 10 mg was sufficient to alleviate the disease Such economy of utilisation may be due to physiologic adaptation to a previously low intake, as apparently happens in the utilisation of calcium It is tempting to speculate that such adaptation might be due to the establishment of alternative metabolic pathways or to better protection of the vitamin by sulphydryl groups or other antioxidants.

Daily requirement for ascorbic acid—Such individual variations in the catabolism of ascorbic acid have resulted in confusion and disagreement about what should be the "recommended allowance" for an adequate normal diet The League of Nations Technical Commission on Nutrition (1938) originally proposed 30 mg daily. The Food and Nutrition Committee of the U S National Research Council recommend (1948) 75 mg This is the only major point of difference between the views of that excellent committee and ours in Britain The Accessory Food Factors Committee of our Medical Research Council, on the basis of the observations cited above (68), sticks to the League of Nations recommendation A committee of the British Medical Association (100) concurs. Perhaps this is a subject on which we can agree to differ, it will take a long time to persuade the naturally conservative British to take tomato juice for breakfast; until they do, perhaps they don't need it!

Ascorbic acid metabolism under stress—Lind saw clearly that the etiology

of scurvy among sailors was essentially related to conditions of life at sea, of which bad food was only part of the picture. In a remarkably modern manner, he was not content with a single etiologic agent, but emphasized also the importance of cold, damp, and fatigue, factors that we now call "stress" The importance of such factors in precipitating scurvy have been recognized by many physicians in this century. Thus, Minot and his colleagues writing (75) about scurvy in 1930 remarked ". . chronic fatigue and excesses of various sorts may precipitate a deficiency disorder when states of nutritional instability are present" As yet, there is no clear evidence that exposure to cold in man results in an increased catabolism of ascorbic acid; under conditions of a well-conducted Arctic expedition with modern equipment, requirements were not increased [Kark *et al.* (76)]. Nevertheless, it is a reasonable assumption that fatigue and exposure to cold contributed in this way to the tragedy of Scott's expedition to the Antarctic in 1910. The rations of that expedition provided no ascorbic acid whatsoever (77). Physical exhaustion, frostbite, and a wound that failed to heal ended in the death of the party that reached the Pole.

The "Burn Assignment" of the Boston City Hospital (78) studied the metabolism of ascorbic acid under another form of stress, severe injuries They showed that in such surgical cases the plasma concentration and urinary excretion of ascorbic acid was markedly depressed and required very large parenteral doses to raise them Andreae & Browne (79) demonstrated that the retention of ascorbic acid by patients suffering from recent burns and fractures may amount to 3 to 4 gm. in the first week, almost as much as a patient with scurvy would require. Their paper includes a good discussion

Ascorbic acid metabolism in infections.—All physicians familiar with scurvy know how often its onset may be precipitated by an infection In recent years, it has been established that infections of many kinds deplete the body's reserves of the vitamin. For instance, Harris and his colleagues (80) followed its urinary excretion in surgical and pulmonary tuberculosis and in osteomyelitis and showed that test doses of the vitamin were retained in unusually large amounts Faulkner & Taylor (81) studied about a hundred patients with a great variety of infections and found that the level of ascorbic acid in their serum was usually well below that of a group of controls, needing unusually large doses to restore it to normal

Naturally, the question has also been asked· does ascorbic acid deficiency lower the body's resistance to infection? Much experimental work has been devoted to the behavior of immunological reactions in scurvy without showing any consistent abnormality A claim that serum complement is reduced in scurvy has been refuted (82); Crandon's complement remained unaffected by scurvy (67). The bactericidal properties of human blood are un-
[illegible] (83)

diseases—This deserves separate
scorbic acid metabolism might be
concerned in the rheumatic process was provided by the careful animal ex-

perimentation of Rinehart (84) in San Francisco, as long ago as 1933. He showed that chronic ascorbic acid deficiency in guinea pigs can produce an arthritis with a striking similarity to rheumatoid arthritis and that experimental infections in such animals resulted in a carditis and connective tissue *changes histologically resembling rheumatic fever* Thereafter, Rinehart and his colleagues (85) showed that the level of the vitamin in plasma of patients

This

udies

of urinary excretion in response to test doses of the vitamin by Harris and colleagues (80) gave further evidence of an increased catabolism of the vitamin in these diseases. Interest in these observations waned when no apparent therapeutic benefit was obtained with the vitamin (see below) Now they deserve re-consideration.

Evidence from the guinea pig—There is, thus, good biochemical evidence that the human body catabolises ascorbic acid in abnormally large amounts following stress, certain infections, and in rheumatic conditions Experimental work on the guinea pig suggests an intriguing explanation of this phenomenon. In 1937, Harris, Passmore & Pagel (87) reported that experimental infections or injections of diphtheria toxin resulted in a considerable diminution in the ascorbic acid content of the suprarenal glands in the guinea pig

The work of Long and his colleagues at Yale has done much to elucidate the influences that affect the ascorbic acid content of the suprarenal cortex. A variety of stresses deplete it, but only if the pituitary gland is intact. Injections of adrenocorticotrophic hormone (ACTH) have the same effect, so that the disappearance of the vitamin from the suprarenal cortex seems to be involved in the general hypophyso-cortical reaction to stress This has been well discussed lately in an excellent review by Sayers (88) in which references to past literature will be found

What happens to the vitamin that disappears from the cortex? Vogt (89) has shown that it does not appear in the suprarenal vein, so that it is evidently not secreted by the gland, either by itself or combined, as has once been suggested, with a steroid Evidently it is destroyed, but in what metabolic process? The reduction in the vitamin is usually accompanied by a reduction in cholesterol, so it might be thought that the vitamin was concerned in the synthesis of suprarenal cortical hormones from cholesterol. Yet scorbutic guinea pigs apparently react normally to ACTH, with the same reduction in cortical cholesterol and a lymphopenia indicating successful *production of cortical hormone. [See Sayers (88)]* Daughaday, Jaffe & Williams (90) have shown that in three patients with scurvy, cortical hormone could still be detected in the urine and did not increase in amount on treatment with ascorbic acid.

At the time of this writing (October, 1950) there is no evidence that ascorbic acid plays a rôle in the synthesis of cortical hormones Yet, it is hard *to reject the idea that they must have a very close metabolic association,*

both have a profound effect on connective tissue—ascorbic acid is necessary for normal collagen formation, while suprarenal gluco-corticoids dramatically relieve collagen diseases, though in a manner as yet to be understood—and both are concentrated in the suprarenal cortex. It is interesting to remember that as long ago as 1933, Lockwood & Hartman (91) reported that cortical extracts, free from ascorbic acid, delayed the onset of scurvy in guinea pigs This observation was confirmed by Ratsimamanga (92).

A further fundamental question remains unanswered and unanswerable at the present time: does ascorbic acid affect the metabolism of connective tissue directly, or by some remote hormonal influence, through the suprarenal cortex and perhaps other glands in which it is concentrated? The answer to this is likely to come, in the end, from the biochemists

Biochemistry of ascorbic acid.—When it was first isolated and identified, biochemists were immediately struck with the ease with which ascorbic acid can be reversibly oxidised and reduced This seemed to assure for it a place in tissue oxidation as an acceptor of hydrogen ions. Other vitamins—riboflavin and nicotinic acid—have since been proved to play such a rôle, but not ascorbic acid Although there have been various claims for the demonstration of an enzymic effect of ascorbic acid in isolated tissues or enzyme systems, these have all proved to be due to the nonspecific result of adding a substance that is easily oxidised Up to the present, students of tissue oxidation have failed to find a specific rôle for ascorbic acid That is not to say that such a rôle cannot be found in the future

A remarkable property of ascorbic acid is that it exists in the human body almost entirely in the reduced state. One of the last researches undertaken by Hopkins (93) was the demonstration that, in the presence of glutathione, ascorbic acid is protected from oxidation until all the glutathione has been oxidised The study of biological antioxidants, such as glutathione, is yet in its infancy It may well turn out that the rapid disappearance of ascorbic acid under stress and infections is a side-effect of some fundamental change in the behaviour of other tissue antioxidants

Therapeutic implications.—The fact that the human body destroys more ascorbic acid in stress diseases, infections, and rheumatic conditions, obviously suggests to the physician that it is his duty to replace it by giving large doses of the vitamin whenever such a process is suspected. The temptation is to push the dosage to achieve saturation so that no tissue possibly in need of it is likely to go wanting It is easy to think of a hypothetical metabolic leak that may be stemmed by the mass-action effect of flooding the body with the vitamin This idea is not new; Hunt (94) recommended that surgical cases should receive 1 gm. daily for three days prior to operation and 100 mg daily thereafter

Yet a word of warning is needed against the random prescription of massive doses of the vitamin As has been said above, the normal human can get along with as little as 10 mg daily, perhaps by establishing alternative metabolic pathways. Who knows that such alternative pathways are not

the ones that need support if the patient is to be helped? The history of medicine has shown repeatedly how easily mistakes can be made by giving treatment on theoretical grounds only. It would be a pity if the prescription of ascorbic acid fell into the same discredit as cupping, purging, and bleeding. In our view, the one clear guide to therapeutics is the age-old one, that of empiricism: does it help the patient, whatever the theory behind it?

Early attempts (86) at treating rheumatoid arthritis with ascorbic acid were not successful. It was recently claimed that doses of 1 gm. of ascorbic acid intravenously (combined with desoxycorticosterone acetate) are beneficial in rheumatoid arthritis (95), but many excellent workers (96) have failed to confirm this. Still more recently, a preliminary report (97) has suggested benefit from even larger doses (4 gm. daily) in rheumatic fever This may prove to be right; yet, sitting here under the Castle rock of this rain-swept city with the last swallow and festival visitor long since departed, amid conditions now ideal for the development of rheumatism, we are not inclined to recommend the indiscriminate prescribing of ascorbic acid beyond physiologic needs and would prefer to wait until the biochemists give us a description of its rôle in intermediary metabolism, leading to an unequivocal demonstration of its therapeutic applications.

POSTSCRIPT

At the end of their article in the 1950 *Review*, Kahn & Stare (98) wrote: "In present day America, nutrition is the single most important environmental factor affecting health " We would not cavil with this judgement as it affects America; it is certainly correct in the great majority of countries in the tropics; but it is not true to-day in Great Britain Whatever the other merits and demerits of the Welfare State in which we live, there is much evidence that the over-all standards of nutrition in our country during the last 10 years have been higher than for many previous generations Although the supply and distribution of our food are not ideal, such deficiencies as there are certainly do not constitute a major cause of ill health or disease A brief summary of the administrative measures introduced to regulate the distribution of our food supplies and a historical account of the factors that lead up to their introduction has been given by Kitchen & Passmore (99). A report by a Committee of the British Medical Association (100) gives an authoritative summary of the present state of nutrition of our people.

The successes of our society in providing suitable food for its members have not been paralleled in housing Too many of our people still have to live in shameful homes We have no hesitation in saying that bad housing is the single most important environmental factor adversely affecting health in Great Britain This, of course, indirectly affects nutrition, since the housewife, struggling to make a home for a family in a structurally inadequate house, has neither the leisure, the apparatus, nor the space to prepare decent meals. Even with a good wage and food in the shops, it is difficult to feed well in a slum.

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ALLERGY[1]

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The advent of adrenocorticotropic hormone (ACTH) and cortisone has created broad inroads into all branches of medicine, and in this the field of allergy is no exception. In point of fact, the effectiveness of these two compounds is probably more promising in the hypersensitive states than in most other conditions for which they have been tried. For this reason, and because a considerable amount of information has been accumulated, this review will be confined to a consideration of the pituitary adrenal mechanism and its relation to hypersensitivity.

It would seem worthwhile to recall some of the earlier observations which were begun as long ago as 1922. For example, the marked decrease in resistance of the guinea pig to anaphylaxis (1) and the fact that species such as the rat and mouse, normally difficult to sensitize, could be easily rendered hypersensitive by the removal of the adrenal glands (2) were among the first demonstrations that these glands were associated with resistance to anaphylaxis. Similar effects were observed following removal of the pituitary (3). Since there is still no clear cut differentiation between immunity and the so-called hypersensitive state, consideration must be given to those mechanisms which appear to be influenced by the steroids of the adrenal cortex and which may be related to either immunity or hypersensitivity or both These may be discussed conveniently under several headings.

Experimental Observations

Pituitary adrenal relations.—The adrenal cortex secretes a variety of steroid complexes which may be divided into three main categories. Of these, the most important group with reference to this discussion is represented by 17-hydroxy-11-dehydrocorticosterone, or as it is now called, cortisone. This substance, which is Compound E of Kendall, and others like it, such as Compound F, influence carbohydrate and protein metabolism primarily. Selye (4) refers to them as the glucocorticoids. They have widespread effects on many other systems associated with hypersensitivity and immunity which will be discussed in the following sections Of lesser importance is the second group of steroids which is represented by 11-desoxycorticosterone or desoxycorticosterone acetate (DOCA) and which is chiefly concerned with electrolyte and water metabolism. This substance, the existence of which in the adrenal cortex is in some doubt (5), has been referred to as a mineralocorticoid (4). Some effects have been ascribed to its administration in the experimental animal and man with reference to hyper-

[1] This review covers approximately the period from October, 1949 to November, 1950.

sensitive states. There is evidence that it may be converted to corticosterone as shown by Hechter *et al.* (6) or that it may be a cortisone antagonist according to Selye (4). The third class of compound is that represented by adrenosterone, which is allied to testosterone and which has androgenic properties. Testosterone has been called the N or nitrogen hormone by Albright (7) and Browne (8) since it exerts an anabolic effect on protein metabolism. Little is known of its relationship to immunity or hypersensitivity.

The metabolic products of cortisone or of the androgenic steroids may be assayed in the urine, thus affording a means of following the relative output of each. When cortisone is secreted by the adrenal or is injected, glucocorticoids increase in the urine. These may be assayed by the method of Venning, Kazmin & Bell (9) or by chemical methods (10). Androgenic steroids, which are derived wholly from the adrenal cortex in the female and in part from the testes in the male, are believed to be converted to the 17-ketosteroids, which appear in the urine as well. The 17-ketosteroids are not as reliable an index of adrenocortical activity as the glucocorticoids, according to Sayers (11). There is as yet no means of measuring DOCA-like activity directly.

The anterior pituitary controls adrenocortical activity by liberating ACTH, which in turn causes hypertrophy of the adrenal cortex. It is probable that an increase in the output of all the various adrenal steroids occurs under the influence of ACTH, although Compounds E and F are primarily affected (12). Thus, it is essential that an adrenal cortex capable of being stimulated be present if ACTH is to exert an effect Cortisone, on the other hand, will act in the absence of an adrenal gland When administered, it probably suppresses ACTH liberation by the pituitary as well as depressing the adrenal itself (13) This latter effect on the adrenal is of importance when considering the differences between ACTH and cortisone administration. Although of no clinical significance as yet, a lyophilized extract of anterior pituitary (LAP) has been used in experimental animals. It is believed to have the properties of stimulating the adrenal cortex to liberate DOCA-like steroids (4). Several excellent reviews on the subject have recently appeared, notably by Thorn (13) and by Sayers (11).

Finally, it may be of interest to note that epinephrine itself appears to stimulate the anterior pituitary to liberate ACTH. That this is due to epinephrine and not norepinephrine has recently been demonstrated by Madison (14).

The eosinophile —The exact function of the eosinophile is unknown This cell, however, has long attracted attention because of its association with allergic phenomena. The peripheral and tissue eosinophilia so commonly found in the majority of patients with manifestations of hypersensitivity needs no comment Because of the original finding of a high histamine content in the cells of rabbit blood and because of the fact that the predominant cell was eosinophilic, Code (81) assumed that the eosinophile

carried histamine. However, in subsequent examination of the blood of patients with varying degrees of eosinophilia, such as is found in periarteritis nodosa, Loeffler's syndrome, tropical eosinophilia, and various forms of allergy, Rose (73, 79, 80) failed to show any correlation between the histamine content and the fluctuations in the eosinophiles. Furthermore, in a patient with tropical eosinophilia, even though the white count was as high as 60,000 per cu. mm. of which 80 per cent were eosinophiles the histamine content was normal and did not vary following ACTH, although the eosinophiles were sharply reduced (73). On the other hand, in the leukemias, particularly the myelogenous variety, Rose (80) observed a parallel reduction in both the markedly elevated histamine content of the blood and the myelogenous cells following x-ray irradiation. These observations, as well as those of Code & MacDonald (82) and Valentine & Lawrence (83), make it almost certain that the eosinophile does not carry histamine

In a recent review, Samter (15) outlined the marked fluctuations in the eosinophilic population of the blood and tissues of the guinea pig following the induction of anaphylaxis. It is interesting to note that whereas an increase in eosinophiles occurs in both blood and bone marrow, the degree of eosinophilia bears no relation to the intensity of the shock Furthermore, according to Samter, sensitization alone without subsequent induction of shock, does not appear to alter the eosinophiles If this be true, it is important in attempting to relate hypersensitivity to the adrenal steroids For example, Dalton & Selye (16) observed a reduction of the circulating eosinophiles during the alarm reaction in the rat at the time when the adrenal was hypertrophied and presumably hyperactive. Speirs & Meyer (17) confirmed the fall of eosinophiles in this species as well as in the mouse following various forms of stress and showed that epinephrine had a similar effect. Removal of the adrenals prevented these changes but the administration of adrenal-cortical extract (ACE) produced them in the adrenalectomized animal. If anaphylaxis in the guinea pig is considered to be an "alarming stimulus," it is evident that the sequence of events in this species differs, since eosinopenia does not occur and, as will be seen below, this would indicate that anaphylaxis in the guinea pig may not be related to adrenal cortical activity

It was Hills and his associates (18) who first showed that the administration of 25 mg of ACTH would produce a reduction of the circulating eosinophiles in man within 4 to 6 hr in the presence of a normally functioning adrenal cortex [illegible]

the factors involved in the control of the eosinophile. Clearly, other factors must be associated as well, and care must be taken in ascribing the commonly observed eosinophilia in hypersensitive states to a hypofunction of the adrenal cortex alone It has been observed that a local tissue eosinophilia occurs in the surrounding area of a wheal induced by the injection of an

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antigen in a suitable subject (19). Since ACTH or cortisone does not usually prevent this type of skin test from occurring even though the peripheral eosinophiles are reduced to zero (78), it is of interest to note that Zeller *et al* (89) noted a reduction in the tissue eosinophilia as a result of ACTH administration.

Lymphoid tissue and antibody formation.—In an impressive set of experiments, Dougherty & White (20) have shown that lymphoid tissue and the circulating lymphocytes of the experimental animal are markedly influenced by the adrenal cortex. Thus the administration of ACTH, or ACE, or the effect of any stimulus to the pituitary adrenal system causes a reduction of the lymphoid mass, and a diminution of the circulating lymphocytes. These findings are similar to those which occur in the first stage of the "alarm reaction" of Selye (21). Dougherty & White consider lymphoid tissue as a storehouse for γ-globulin, and with lysis of the tissue, γ-globulin may be released according to their observations (22). This is an important concept since it is now established that antibody is modified γ-globulin (23). Under the influence of ACTH or cortisone, an increase in the antibody titer of an immunized animal might be expected to occur, and White & Dougherty reported results in support of this attractive theory. In more recent studies, White (24) has shown that the *in vitro* release of antibody from tissue is influenced by the adrenal cortex, for a greater release was observed from the tissue of animals previously injected with ACTH as compared with that from nontreated controls. In this connection, it may be well to remember that resistance to anaphylaxis or other immune mechanisms is not invariably associated with an increase in the antibody titer of the serum as was once thought.

Further investigation of the problem has revealed not only negative results, but a reversed relationship. For example, Eisen and his co-workers (25) were unable to demonstrate an increase in the antibody titer or γ-globulin of the sensitized rat following ACTH, although dissolution of lymphoid tissue and reduction of the circulating lymphocytes did occur Similar results were observed by Li & Reinhardt (26) as well as others (27, 28). Both Mason *et al.* (29) and Forsham *et al.* (30) failed to increase γ-globulin in man by repeated administration of ACTH. The same is true, apparently, for circulating antibody as first demonstrated by Herbert & deVries (31) and confirmed by others (32). Although the significance of the increased amounts of γ-globulin in the serum of patients with lupus erythematosus is not clear, it is of interest that Reiner (33) was able to demonstrate a return to normal of the γ-globulin in five patients with this disease during ACTH therapy. Recently, Germuth & Ottinger (34) have observed a similar relationship, for on the administration of ACTH or cortisone to sensitized rabbits, antibody titer could be suppressed to zero More interesting was the fact that the Arthus phenomenon was also suppressed at the same time, and the two phenomena ran parallel It is of further significance that, in rabbits treated with ACTH or cortisone, the Arthus phenomenon could still be

produced by the method of passive transfer, indicating that so long as both antibody and antigen were present, the cellular reaction could occur. Thus, the suppression of the reaction cannot be at the cellular level if these results are correct. These findings support the observations of Murphy & Sturm, who in 1947 (35) observed a marked increase in the antibody titer of adrenalectomized animals. Thus, in sensitized rabbits with an excess of cortisone, antibody production may be prevented, whereas in the absence of the adrenal, there is a marked overproduction of antibody.

This, then, throws a different complexion on the argument, for logically enough, if there is no antibody for antigen to combine with, there can be no allergic reaction. It would be surprising, however, if the protection afforded by ACTH against certain bacterial infections such as the *Pneumococcus*, as shown by Finland *et al* (36), were based on a similar mechanism, and it is noteworthy that the development of specific antibodies did occur in the patients observed by them One is tempted to believe that these findings may be part of the answer to the riddle of hypersensitivity and immunity. For example, if the adrenal suppressed those antibodies concerned with such lesions as the Arthus phenomenon, bacterial hypersensitivity, and the like, but did not interfere with those associated with resistance to infection, one might postulate a difference between the susceptibility to hypersensitivity on the one hand and the induced state of immunity on the other, depending on the pituitary-adrenal response. It will be obvious, however, that this intriguing aspect of the problem still requires clarification, for, as will be seen below, there are still a number of observations which are difficult to reconcile with this concept.

The reticuloendothelial system.—Clear cut experimental evidence showing a direct relation of the adrenal cortex to the reticuloendothelial system was lacking until recently. It had been shown by various workers that removal of the adrenal gland caused either an increase or decrease in the activity of the macrophage system or the other components of the reticuloendothelial system (37, 38)

Reiss & Gothe (39) in 1937, using the then available preparation of ACE, showed that the Kupffer cells of the rat were able to take up more foreign particulate matter, such as lithium carmine, than were those of the non-treated animal In a recent series of experiments, Gordon & Katsh (40) have confirmed and amplified these findings. Using both chemical and chromatographic methods, they have been able to demonstrate quite clearly that the ability of the rat spleen to take up thorium is under the direct influence of the adrenal cortex. An examination of the macrophages and phagocytes showed a reduction in both numbers and size following extirpation of the adrenals. In this connection, it is of interest that Dougherty & White (41) observed the converse, namely, an increase in the numbers of phagocytic cells in lymphoid tissue following increased adrenocortical function White (24) comments on the similarity of this picture to that seen following the injection of a bacterial antigen. However, Spain, Molomut & Haber (85)

have recently noted that cortisone administered to mice markedly retards the macrophage response, for when carbon particles were injected intraperitoneally, there was little attempt at removal, whereas in controls, most particles had been removed from the peritoneal cavity and could be found in the lymph nodes. One is again faced with controversial findings which might be explained on methods and species differences.

Histamine and anaphylaxis.—Among the alterations observed following the administration of histamine, Dale & Laidlaw (42) noted a striking similarity to those characteristic of anaphylactic shock and postulated that histamine may be released during anaphylaxis, thus accounting in part for the shock-like state. The subsequent confirmation of this theory is now well known and need not be elaborated upon here save to emphasize the close relation between the two states In 1920, Dale pointed to the adrenal as a controlling factor in both histamine and anaphylactic shock (43) Shortly thereafter, it was observed that removal of the adrenals markedly reduced the resistance of experimental animals to histamine (44). The mechanism whereby this loss of resistance occurred was elucidated in part by the experiments of Rose & Browne (45), who showed that the capacity of rat tissue to inactivate or destroy injected histamine was dependent on the presence of an intact adrenal. Of perhaps greater interest was the finding that the histamine content of normal tissue was increased by as much as two to three times following adrenalectomy (46). It was subsequently noted by Karady, Rose & Browne (47) that histaminase, an enzyme which destroys histamine, was depressed following removal of the adrenals, thus accounting in part for the accumulation of the histamine in the tissues. These findings supported early demonstrations that resistance to histamine intoxication as well as to anaphylaxis is impaired following adrenalectomy in this species (47). Although the egg-white reaction in the rat requires no previous sensitization, being induced by a single injection of egg albumen (48), it appears to be dependent in part on histamine release since it can be inhibited by the previous administration of an antihistamine compound (49). Of particular interest, therefore, is the fact that Selye (50) has shown that this reaction, which resembles angioedema in man, can be inhibited either by cortisone or ACTH. It should be emphasized that this phenomenon is a so-called "anaphylactoid" reaction and requires no previous sensitization.

The guinea pig presents a different picture. This species, which has been repeatedly used for the classical demonstration of anaphylaxis, is said to become more susceptible to anaphylactic shock following removal of the adrenals (1). That histamine release is part of the syndrome has been amply verified (51, 143) It was not surprising, therefore, to find that the previous administration of an antihistaminic would protect this species against [illegible], Leger, Leith & [illegible] treatment with [illegible]andau (55) and Friedlaender & Friedlaender (56). It should be pointed out that in all of

these studies, the animals were first sensitized and the usual incubation period allowed for antibody formation to take place. ACTH was administered over a period of hours prior to the injection of the shock dose. Possibly ACTH administration prior to the sensitizing dose and during the incubation period might prevent antibody formation and susceptibility to shock. The latter workers (56) were also unable to increase resistance to histamine either by ACTH or cortisone administration.

Beginning with the demonstration by Katz (57), liberation of histamine by the combination of an antigen with its specific antibody *in vitro* has been confirmed many times To these have been added the observations of Spain, Strauss & Neumann (58), who have noted that combination of ragweed antigen with its antibody may also release histamine from cells which contain it. Of considerable importance, therefore, was the attempt of Carryer & Code (59) to inhibit *in vitro* histamine release by cortisone. They had shown that the production of a hemolytic reaction by the addition of sheep erythrocytes to the blood of appropriately sensitized rabbits resulted in a release of histamine (60). On addition of cortisone to the mixture, there was no inhibition of the histamine release This might be compared to the experiments of Germuth & Ottinger (34) previously described, since neither ACTH nor cortisone prevented union of antigen with antibody and the subsequent events.

It should be emphasized that histamine release is not an invariable result when antigen and antibody combine. For example, the explosive anaphylactoid reaction brought about by the injection of Forssman antibody into the the guinea pig is not accompanied by the release of histamine (61) nor is it inhibited by the administration of antihistamine compounds (62). It seems also fair to say that many other conditions which are thought to depend on the combination of antibody with antigen, such as the production of periarteritis in the rabbit by the injection of horse serum as demonstrated by Rich & Gregory (63), fall into the same category. One is faced with the same problem in man, for here the role of histamine in the hypersensitive states is based with few exceptions on the efficacy of antihistamine compounds. As is well known, the use of these is limited to rhinitis, acute urticaria, and the drug reactions in the main (64) Attempts to demonstrate a release of histamine have been for the most part unsuccessful (79) In recent studies, by means of cardiac catheterization, Rose, Rusted & Fownes (65) were unable to show any increase in the histamine content of the blood taken from the pulmonary artery, as well as from the femoral, during induced attacks of asthma

There are certain aspects of the problem which implicate histamine nevertheless For example, it has been noted that whereas the urine of normal subjects contains little or no histamine, moderate to relatively enormous amounts have been found in the urine of asthmatics (66). In an assay of the histamine content of antral mucous membrane and lung tissue, Rose, Entin & Baxter (67) have observed higher amounts in the tissues of allergic

individuals than is found in nonallergic subjects. There are also the findings associated with pregnancy. Derbes & Sodeman (68) drew attention to the fact that pregnancy is associated for the most part with a disappearance of asthma in patients so afflicted, although this is not invariable. Rose, Harkness & Forbes (69) studied the histaminase activity of the plasma in a series of pregnant women, most of whom were free of allergy and some of whom suffered from asthma or atopic eczema despite pregnancy. It was found that whereas the histaminase complement of the plasma was increased to the usual extent in the normal patients, there was a reduction from the normal levels in those whose allergy continued. Of great interest at the time was the observation of Venning (70) that the adrenal cortex is hyperactive in pregnancy as evidenced by a marked increase in the urinary excretion of glucocorticoids. Although an insufficient number of asthmatic subjects were observed, there was some evidence that the glucocorticoid excretion was also impaired. These findings together with the results on animal studies pointed to a further relation between the adrenal cortex, histamine, and hypersensitive states.

Finally, it should be noted that, whereas most of the above mentioned changes following extirpation of the adrenal glands were only partially restored by the administration of DOCA, complete restoration in most instances was achieved by the injection of ACE (40, 145) which contains Compound E as well as other active substances

The Clinical and Metabolic Effects of ACTH and Cortisone in Hypersensitivity

In view of the fact that the only adrenal steroid available in quantity was DOCA, initial attempts were made to treat various forms of allergy by the administration of this compound (71). The results were very controversial, and this form of treatment was soon abandoned. With the advent of ACTH and the observations of its remarkable capacity to stimulate the adrenal, initial studies were carried out by Herbert, deVries and Rose (72, 73) on a patient with Loeffler's syndrome in 1947. In addition to the reduction in the eosinophilia, a remission was produced. In view of the spontaneous remissions which are characteristic of this disease, the possibility that the [illegible] considered as certain

observations on hypersensitive states were begun independently in 1949 by three groups of workers. These were Bordley *et al.* (75, 86), Randolph & Rollins (76), and Rose *et al.* (77)

Virtually every allergic state, including asthma, rhinitis, hypersensitivity to drugs, urticaria, atopic eczema, vernal conjunctivitis, inflammatory diseases of the eye, and those conditions which form the group of collagen diseases such as periarteritis nodosa, lupus erythematosus disseminata, scleroderma, and dermatomyositis, and finally rheumatic fever, have been in-

vestigated by the use of ACTH and cortisone. Space does not permit a complete description of all these results, and only those conditions which are known to fulfill all the criteria of allergy will be dealt with.

Asthma.—As the most distressing and frequent of all the common forms of allergy, asthma has received the most attention. Studies have beer reported by Bordley *et al.* (75), Randolph & Rollins (76, 87, 88), Carrer *et al.* (90), Elkinton *et al.* (92), Samter (93), Thorn *et al.* (98), Astwoo *et al* (91), McCombs *et al* (100), Carey *et al.* (101), and Rose *et al.* (7, 78) Using ACTH, most investigators have observed a rapid disapper ance of all signs and symptoms, beginning sometimes within 24 hr. bı usually taking 48 to 72 hr. Complete disappearance takes place anywhe from 36 hr to 14 days. The duration of remission following cessation of th apy seems to vary considerably according to different observers. For ex ple, in the 23 cases reported by McCombs *et al.* (100), it varied from days to 4½ months. On the other hand, the variation was 3 days to a roximately 9 months in the series of 19 patients followed by Carey *et al.* (1) An attempt to distinguish between the response of a so-called pure "ext isic" asthmatic and the older "intrinsic" asthmatic can be made only wit difficulty at this time. Carey *et al* (101) had four mixed cases in their g up, two of which failed to respond to therapy. In a series of 50 asthma s studied by Rose *et al.* (95), there appeared to be some difference, for the intrinsic type remissions appeared usually by the fourth or fifth da t the latest, and the patients remained clear for only three to five weel in all instances. The only cases in this group which failed to remit were t e who had marked obstructive emphysema. In the "extrinsic" group, a ough the disappearance of symptoms could be as rapid, it was sometimes layed as long as 10 days or did not occur at all. After cessation of the y, the patients remained free for periods varying from several weeks to long as nine months. Rose *et al.* (94) also observed that the duration of atment seemed to bear no relation to the duration of remission, in that ur days proved just as effective as ten days treatment. Further obser ions are necessary, however, before the ideal regime may be clearly def .

Several groups of investigators have n d the effects of repeated courses of therapy. Both McCombs *et al.* (100) a arey *et al.* (101) found an equally good response with a second and th trial However, Carey *et al* (101) observed that the asthma, prior to st ng the second course, had not attained the degree of severity presen efore the initial course Rose *et al.* (94), on the other hand, have freq ly noted that a second course does not produce as salubrious an effec the first one, although this is *not a* constant finding

Cortisone has been used less uently than ACTH It may *produce the* same end result, but it takes lc to act in that at least four *to five days* are required before the sign d symptoms begin to *disappear. In the* experience of Carey *et al* (101 ly one of the five patients *treated obtained* a complete remission by th h day. None of the oth*ers were completely*

relieved, although there was definite improvement. Rose et al (94), us the same patients, gave ACTH for the first course and cortisone for . . . They found that with cortisone, complete freedom of sympto

of thera . . he pollen count remained high. Their dosage was relatively smal long as t . . of Similar results were reported by Randolph & Rollins (87) wh however . . ent therapy for 48 hr. only.
maintained . . hou . pears to be little doubt that treatment in hospital is much more

There a . . e . . as scan that given on an ambulatory basis. For example, it has efficacious th . . findity noted that whereas a course of 100 mg. ACTH per day in been repeated . . tion beill produce a remission and maintain a patient easily in hospi- divided doses w . . 90 mg ACTH given daily to the same patient on an ambula- tal, as much as 2 . . uld be ill to alleviate symptoms (94). This may be due to the fact tory basis may fa . . xtirpatiare used in hospital, whereas a single injection of the long that divided doses . . nistratio rule for ambulatory patients because of its convenience acting ACTH is the . . by themilar results have been observed using cortisone. In a On the other hand, s . . s other ting first in hospital with a dosage of 200 mg cortisone group of patients, trea . . METABC . . and following with 100 mg. a day for an additional for the first three days . . ission was achieved by the fifth to seventh day, four days, complete rem . . IN H . . for 14 days has failed to produce a remission out whereas 200 mg cortison . . at the hat much longer periods of observation are neces- of hospital It is obvious t . . ts were e problem is clarified.
sary before this aspect of th . . mpou syndrome, which some consider to be an inter-

Loeffler's syndrome —Thi . . ent it and periarteritis nodosa, was first investigated mediary stage between asthma . . (f its 73) Using 120 mg ACTH in divided doses, in 1947 by Herbert et al (72, . . ied (of the pulmonary infiltrations after 24 hr there was evidence of clearing . . on . . ndrol have been observed by Rose et al (94) Since that time, two other case . . was . . sions cleared just before the patient was In one of these, the pulmonary . . of t . . re asthma persisted A good response to admitted to hospital, although sev . . ACTH . . nt has remained free of symptoms for ACTH was obtained, and the patie . . ts . . (74) severe asthma, rhinitis, and polyps, nine months A second patient with . . of . . shifting pulmonary infiltrations by who had the marked eosinophilia and . . re . . dmitted to hospital On admission, x-ray for many months, was finally a . . ey . . asthma severe, the chest showed although the eosinophiles were high an . . g a . . scular markings This patient was little else other than increased bronchovas . . co . . sti . . tion was cleared by the adminis- very resistant to ACTH until a sinus infect . . ting two weeks only, after which tration of terramycin He had a remission las . . the . . se cases are too few to warrant intractable asthma returned The data on the . . rheu . . m sonal rhinitis were reported any conclusions at this time . . mijins (88) Rapid disappear-

Allergic rhinitis (seasonal) —Studies on sea by Carryer et al (90, 141) and Randolph & Ro

ance of symptoms was observed with remissions lasting from four days to several weeks It is of interest to note that the symptoms of asthma in the cases treated by Carryer and his co-workers disappeared more rapidly than did those of the hay fever

Allergic rhinitis (nonseasonal with polyp formation).—According to Bordley *et al.* (75), nonseasonal rhinitis with polyp formation responds to ACTH therapy with a shrinking of the nasal mucous membranes and a complete disappearance of the polyps. Rose *et al.* (78), on the other hand, also noted shrinking of the membranes with a return of normal appearance, but in no instance did the polyps completely disappear. The changes usually come about in two to seven days after the initiation of therapy, and remissions have been observed for one to three months Climate may be a factor, for in one patient, after the first course of ACTH, which was in the month of February, the remission lasted for one month after which symptoms returned Following the third course in June, he remained symptom free until the first week of September. Allergic cough, which is often associated with the above condition, responds very quickly as well In a recent report, Bordley (96) has described the changes following ACTH or cortisone in a series of 57 cases of which 20 had asthma and nasal allergy and only one had rhinitis and marked polyp formation alone Although changes were apparent 24 to 72 hr. after the institution of ACTH, it generally took two weeks for the complete disappearance of polyps. The changes were delayed some 24 hr. on cortisone In all but three patients, nasal polyps reappeared within two weeks to three months after either form of treatment. Bordley also described slow but definite regression of polyps using a nasal spray consisting of 8 mg of cortisone per cc three times daily.

Urticaria and drug reactions.—Of seven patients with acute urticaria associated with angioedema proceeding to the chronic state, some of which had ACTH or cortisone for as long a period as two weeks in doses comparable

former had a moderate eosinophilia before treatment whereas the latter had

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been sensitive to very small amounts. Of considerable interest were the

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Urticaria and drug reactions—Of seven patients with acute urticaria associated with angioedema proceeding to the chronic state, some of which

has also been noted (94). Several observers have noted that the flare and wheal induced by the intradermal injection of histamine is also unaffected (97, 99).

On the other hand, the delayed skin test typified by the tuberculin reaction can be completely inhibited. Thus, Long & Favour (123) were able to inhibit the tuberculin test in 13 and the β hemolytic streptococcus reaction in 19 of a total of 34 patients. It took from 3 to 30 days for complete disappearance, and the reaction reappeared within 7 to 28 days after cessation of therapy. It is of interest that this is the time it takes for many of the intrinsic asthmatics, in whom infection frequently is a factor, to exacerbate after treatment with ACTH or cortisone. As noted in a previous section, the Arthus phenomenon appears to be inhibited by the administration of cortisone (34). It is of interest here that Soffer *et al.* (124) were able to inhibit the Shwartzman reaction when ACTH was administered preceding the provocative injection of bacterial filtrate. When ACTH was injected prior to the preparatory injection of bacterial filtrate, it had no effect on the reaction. These results are difficult to interpret at this time

Dosage.—It will be obvious from reviewing the literature that no hard and fast rule can be used in guiding one as to the correct dose to use in any one patient For example, Thorn *et al.* (98) recommend 5 to 20 mg. ACTH every six hours as the minimal effective dose. On the other hand, as much as 200 mg. ACTH produced no untoward effects when given intravenously to an experimental subject (136).

Most investigators have used the Armour preparation of ACTH in four divided doses given at intervals of six hours intramuscularly, the average daily dose for most conditions being 100 mg However, variations of from 40 to 150 mg. daily have been reported It has become increasingly apparent that no two patients act alike, and one has to gauge the dose by the clinical response of the patient primarily and the appearance of side reactions In hospitalized patients, 100 mg. in four divided doses brings about a reduction of the circulating eosinophiles usually to zero within the first 6 to 12 hr. After the first three days at this level, the daily dose may be decreased to 75 or even 50 mg per day in some patients. The duration of therapy has been varied, some treating for four days only (78), others for as long as 21 days in the ordinary types of allergy, such as asthma and rhinitis (100, 101).

With cortisone, most observers have employed a single daily injection intramuscularly. Schedules varying from 300 mg for two days followed by 200 mg for an additional nine days, to 200 mg on the first day followed by 100 mg thereafter for seven days were used by Carey *et al* (101). Rose *et al* (94) have administered 300, 200 and 100 mg on the first, second, and third day respectively, followed by 100 mg thereafter Thorn *et al.* (98) observe that "in general Cortisone in daily doses of 50 to 200 mg produces a much less striking fall in circulating eosinophiles than ACTH in doses of 40 to 100 mg daily, although the clinical response may be identical." In this connection, Carey *et al* (101), using ACTH, noted a striking correlation between

the day that complete remission from asthma was observed and the attainment of the maximal fall in eosinophiles McCombs *et al* (100) using Astwood's preparation (137) or a similar one prepared by the Wilson Laboratories used a dosage of from 10 mg three times daily to 40 mg. six times daily. It should be noted that this type of ACTH (corticotrophin) is about twice as potent as the Armour preparation and had to be administered subcutaneously, since intramuscular injections were painful

In ambulatory patients, Rose *et al* (94) have found that larger amounts of both compounds may be required to produce an effect comparable to that achieved in the same patient when in the hospital As much as 200 mg. of long acting ACTH (ACTH with a diluent which retards absorption) or 200 mg of cortisone daily may sometimes produce a reduction in the circulating eosinophiles, although seldom to the same degree as with the smaller doses in hospital Similarly, a disappearance of symptoms is not achieved as easily. The reasons for these discrepancies are not apparent unless it be that more of the compound is required because of the activity of the patient Thus, in observing the effect of physical exercise on the output of urinary glucocorticoids in healthy subjects, Venning *et al* (134) noted a marked increase following a route march, as compared to resting output levels. Another factor, of course, may be that allergic patients always do better when away from their home environment

Side reactions—The side reactions associated with the use of either of these compounds depend to some extent on how they are used. A close check on such things as the state of the lungs, the blood pressure, presence of edema, and other clinical phenomena may prevent most of the untoward reactions which have been reported These include transient hypertension, dyspnea associated with beginning of heart failure, edema of the ankles, acne, moon facies, hirsutism about the face, psychic changes, and occasionally pigmentation of the skin and nails (98, 125).

The transient hypertension which is seen with both preparations is not common It, as well as the gain in weight which occurs by the third or fourth day of treatment, is explained by the sodium chloride and water retention which not infrequently occurs and may readily be alleviated by reducing the salt intake of the patient (94, 100, 101) It is generally in the patient who is treated for a longer period of time that moon facies or acne may be produced, but neither of these changes is permanent Occasionally, potassium depletion may occur, but this is in the rare case Checks on the blood potassium or an occasional electrococardiogram will reveal the condition before such symptoms as muscular weakness are observed. A potassium supplement may be given orally if necessary

Although urticaria or other manifestations of drug hypersensitivity are not produced by cortisone, they have been observed with the use of ACTH (98) This is not surprising when one considers that ACTH is an extract of pituitary It may seem surprising, however, in view of the antiallergic properties of both compounds However, as noted above, urticaria from other causes

does not seem to respond to either ACTH or cortisone with any degree of success. In two cases observed by Rose *et al.* (94) where urticaria occurred during ACTH therapy, prompt remission was produced on switching to cortisone.

In some patients, the administration of cortisone may be followed by *severe pain at the site of injection* without redness or heat. Such patients are markedly incapacitated, and as a general rule treatment with the compound has to be terminated. Similar findings have been observed with the use of long acting ACTH (94).

Of perhaps greater import is the masking of symptoms of perforated duodenal ulcer while on ACTH treatment as reported by Beck *et al.* (110). This patient, a case of periarteritis nodosa, while under treatment developed pain in the left epigastrium and complained of a feeling of some fluid in the abdomen. There was no initial increase in temperature or white count. Twenty-four hours after the onset, the temperature had risen to 99.8°F., and there was an increase in the leucocyte count. On examination, there was diffuse tenderness which could not be accurately localized. At operation, the abdomen was filled with pus, but the intestines and omentum appeared quite healthy. After careful exploration, a small, clean-cut perforation without any signs of surrounding inflammation was located in the duodenum The surrounding tissue was perfectly normal, and there was no attempt on the part of the omentum to surround the opening. Here, then, was an example of an acute perforation without any of the usual responses to infection. The patient was sewed up and made a good recovery, although ACTH therapy was maintained There was no interference with healing.

Metabolic changes.—The metabolic changes occurring before, during, and after treatment with either ACTH or cortisone were studied by Rose *et al.* (*78, 126*) in 18 patients with allergy. Several other metabolic studies in allergic patients have been reported by Sprague *et al.* (127), Elkinton *et al* (92), and Samter (93) With the exception of the marked histamine excretion in the urine which, as a rule, does not occur to any great extent in normal subjects, there is little to distinguish the allergic patient from the other types of syndromes which have been investigated In general, following the administration of ACTH there is an increase in the urinary output of glucocorticoids and chemical corticoids, 17-kestoteroid excretion, urine histidine excretion (74), urinary uric acid excretion, a marked increase in the ascorbic acid excretion, usually but not invariably a retention of sodium and chloride, and an increase in potassium excretion. The notable difference between these findings and those which occur with cortisone is the absence of a rise in the 17-ketosteroids, although there is some controversy about this point (11). Evidence of a lowered glucocorticoid excretion in the con-
[illegible] has been noted by Venning, Johnson & Rose (12[illegible]

tissue eosinophiles have been referred to above. Some but by no means all of the subjects who were studied by Rose *et al.* (94) went into negative nitrogen balance It is of interest that Schwartz & Engel (129) have observed that ACTH or cortisone reduced the plasma amino peptidase where pretreatment levels were high, and a clinical remission was produced.

Contraindications.—One of the contraindications to therapy in the asthmatic may be the presence of marked obstructive emphysema, a condition which may present difficulties of diagnosis In studies on respiratory function, most observers have relied on the maximum breathing capacity and the vital capacity (76, 93) As is to be expected, with the temporary state of emphysema which all asthmatics manifest, both of these indices return to normal as the patient improves on therapy. In addition to these studies, however, Pump *et al.* (95) made observations on the residual air. This measurement of pulmonary function offers a more accurate means of following the changes in the lung during treatment and is also of value in the diagnosis of emphysema as such In those patients who did not respond to treatment, there was no reduction of the residual air. However, the initial value was usually higher in those patients who failed to respond as compared to those who did not. Another feature of these studies was the constancy of the measurements in true emphysema as compared to the somewhat fluctuant ones of the true asthmatics with temporary emphysema. Patients with marked obstructive emphysema may become more dyspneic on treatment, possibly because of the increase in the blood volume at the time. Another contraindication is said to be the presence of diabetes mellitus. In this connection, Rose *et al* (94) have now treated one diabetic for 10 months He required daily insulin and had severe rhinitis with marked polyp formation. He has had four courses of treatment, one of ACTH while in the hospital and three subsequent courses of cortisone. During treatment, the glucose tolerance was markedly impaired, but this returned to its former state following withdrawal of therapy each time. Recently, the patient's insulin has had to be increased from 25 units of protamine zinc insulin to 30 units daily. Another patient with asthma and diabetes mellitus was given a course of ACTH in the hospital Again there was a [illegible]

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which occur in the hypersensitive state following the administration of ACTH or cortisone mark a great advance in the understanding of the underlying disease processes involved It is clear as well that these compounds, properly used, will take their place at the head of the therapeutic armamentarium available for the treatment of allergic diseases However, it is too early to state with any degree of certainty how the various disease entities are altered, or that the common forms of allergy and the collagen diseases are actually manifestations of hypoadrenal function There is evidence in favor of this conception in some of the conditions which have been studied. For example, a lowered urinary output of glucocorticoids in the "intrinsic"

asthmatics has been noted. In addition, there is the usual weight loss, tendency to infection, and eosinophilia. These are the cases which Rackemann has called examples of "depletion" (130). In many, there is a lowered output of the 17-ketosteroids as well (128). In the younger asthmatics, neither the glucocorticoids nor the 17-ketosteroids are depressed to the same extent, and they may be well within normal limits.

An eosinophilia by itself cannot be taken as the *sine qua non* of impaired adrenal cortical function, although it is quite conceivable that in allergic states, such may be the case. Patients with severe asthma and eosinophilia of a marked degree may respond to ACTH or cortisone with the disappearance of symptoms and a reduction of the eosinophilia. On cessation of therapy, even though the asthma does not return, the eosinophiles may climb back to an even higher level than before treatment. It is difficult to reconcile these findings with the concept that both are due to the same inadequate output of cortisone.

Then, there is the disturbed histamine metabolism, which is perhaps of more significance if one assumes that this metabolite is involved in the production of symptoms associated with the common forms of allergy. For here, the presence of an increase in the histamine content of tissues following extirpation of the adrenal glands in animals (46) as well as the increased susceptibility to both histamine and anaphylaxis (1, 2) is not dissimilar to the increased histamine content of certain tissues of allergic man (67) and the increased sensitivity of the "shock tissue" to such agents as histamine and mecholyl (65). The predominant effects of histamine are smooth muscle contraction, increase in capillary permeability, dilatation of arterioles and venules, and stimulation of glandular secretion. These changes are characteristic of the common forms of allergy but cannot be said to pertain to those alterations characteristic of the collagen diseases (143) The administration of ACTH or cortisone is often followed by an initial increase in the histaminuria in allergic patients followed by a gradual decrease in some patients to zero (77). Since histaminuria is not generally found in nonallergic patients, these findings could be related to a hypoadrenal state, but again this is an assumption at present. Since histidine is a precursor of histamine, the increase of histidine in the urine of patients following the administration of ACTH or cortisone, as shown by Rose *et al.* (78) and Holbrook *et al* (131), could mean that less histidine was being converted to histamine under the influence of increased output of adrenal cortical steroids

With reference to the collagen diseases, Rich and his school (63) have amply demonstrated that periarteritis and rheumatic carditis are manifestations of hypersensitivity, and this has now been confirmed by others many times. Thus, the injection of a single massive dose of horse serum will induce the production of these lesions in the rabbit The clinical syndrome in man may follow the administration of drugs In contrast to this "foreign protein" arteritis, Selye (132) has demonstrated the production of periarteritis in the rat with unilateral nephrectomy by the prolonged injection of DOCA associated with a high salt intake. These latter lesions may be pre-

vented if cortisone or ACTH is administered at the same time, again illustrating the antagonism between DOCA and cortisone (4). No reports have been encountered in which periarteritis or rheumatic lesions have been produced in the rabbit by the administration of DOCA or in the rat by the injection of foreign protein. An attempt to find a common denominator in the pathogenesis of DOCA arteritis and foreign protein arteritis was unsuccessfully attempted by McLean & More (133). It is possible that both mechanisms are involved

As to the relation of hypersensitivity to the General Adaptation Syndrome of Selye, there appears to be as much evidence against as for the hypothesis that these clinical entities are diseases of adaptation. One knows of the factor of heredity in allergy, to consider the common forms first. The child of one month who develops atopic eczema and intractable asthma can hardly be considered an example unless he be born with a malfunctioning pituitary adrenal mechanism. The seasonal allergic, whose corticoid and 17-ketosteroid excretion is within normal limits and who has an eosinophilia and symptoms during the pollen season only, as shown by the charts of Randolph & Rollins (87), does not surely develop hypoadrenal function during this time of the year only, unless it be that the strain of asthma with its attendant sleeplessness demand a higher output of cortisone from an adrenal which is incapable of meeting the requirements. It is in the older asthmatic whose symptoms have been present for years that the evidence is more convincing as stated above. However, there appears to be some block in the transmission of the stimulation to the pituitary adrenal mechanism in all such patients, for there can be no doubt that acute asthma or generalized eczema must constitute a stressful situation which, if one assumes that the general response of the body is one of increased adrenocortical secretion, should stimulate the pituitary adrenal mechanism. That this does not occur seems to be the case, for in the cases observed by Rose *et al.* (94) who were in severe asthma during the control period of observation, the glucocorticoid excretion was either within normal limits or lower than normal (124). This does not establish that the adrenal is not capable of responding, because it is in such pat ents that symptoms may disappear following surgical operation, and this is one condition described by Weil & Browne (138) where the output of glucocorticoids may be markedly increased It would, of course, be necessary to observe the excretion of glucocorticoids in an asthmatic under the above conditions in order to prove this point There is again the variation in the demands of the body for cortisone. Reference to the fact that physical exercise increases the output of urinary corticoids has already been made (134) This may explain the finding that larger quantities of ACTH or cortisone may be required to maintain asthmatic patients who are ambulatory as compared to when they are hospitalized.

If, according to Selye (50), one assumes that the pituitary becomes "derailed" so that a stressful stimulus produces the release of another hormone which results in the secretion of increased amounts of DOCA and inadequate amounts of Compound-E-like steroids from the adrenal cortex, does it follow

that hypersensitivity may result? The experimental evidence for this in relation to the "egg white" reaction has already been quoted. However, it was once the fashion to treat asthma by the administration of DOCA (71). In some quarters, it was felt that there was improvement in the clinical status of the patients, but for the most part, this form of therapy has been abandoned. None the less, no cases were reported in whom symptoms were exacerbated. It should, perhaps, be noted that according to Selye (4) "in general, the diseases of adaptation are not due to a deranged hormone production as such but to an abnormal humoral response to stress" In spite of these discrepancies, there is no doubt that the concept of the "alarm reaction" and the "General Adaptation Syndrome" have stimulated a great deal of thought and experimental work in an effort to support or deny the general theory.

Several theories have been advanced in an effort to explain the mechanism whereby ACTH and cortisone may exert their effects. Dougherty (135) suggests that the release of the anaphylactogenic substance which results from the combination of antigen with antibody may be interfered with. Since, in the experimental animal at least, histamine plays a prominent role in the production of symptoms, it could be regarded as the agent in question. One strong argument against this possibility is that ACTH or cortisone does not inhibit the Arthus phenomenon when *it is induced by the* method of passive transfer, for as noted in a previous section, the effect of cortisone must be directed to that stage in the process which antecedes antigen antibody combination. To reduce the effects of ACTH and cortisone to the alterations in histamine metabolism seems, at this point, similar to the original controversy as to the role of the adrenal in the regulation of *carbohydrate, potassium, and electrolyte metabolism,* the proponent of each theory placing the essential role of the gland as functioning primarily to that end (5).

It is difficult to disregard the fact that ACTH and cortisone pre-eminently mask the disease process in the majority of the conditions in which they have been tried. It is also obvious, as emphasized by Samter (93), that following withdrawal of therapy, the underlying disease process remains The asthmatic who is rendered completely free of symptoms will eventually exacerbate in precisely the same way and in the same tissue. Be that as it may, this new era in medicine and in allergy in particular has opened many new avenues of approach to the problem, and it is not too optimistic to hope that before long, the actual cause of the tendency for a subject to become allergic, which basically is the heart of the problem, may be unearthed.

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DISEASES OF THE REPRODUCTIVE SYSTEM[1]

By Warren O. Nelson
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THE TESTIS

Remarkable progress has been made during the past decade in the diagnosis and treatment of the testicular deficiencies which are responsible for eunuchoidism and infertility. The knowledge which has been gained concerning the infertile male is of particular importance in view of the fact that in no less than 40 per cent and probably in more than 50 per cent of all infertile matings, the male partner is wholly or partially responsible for the lack of conception. The progress in our understanding of testicular defects has been the direct resultant of the correlation of structure and function with human males as subjects for study, thus avoiding errors of translating animal investigations in terms of human reproductive physiology. The insight into the dynamics of reproduction in the human male was made possible by the development of two diagnostic technics: (*a*) assessment of testicular biopsies [Charny (1, 3), Hotchkiss (2), Engle (4), Nelson & Heller (5)]. and (*b*) the assay of urinary gonadotrophins [Heller & Chandler (6) Jungck, Maddock & Heller (7), Klinefelter, Albright & Griswold (8)]. Thus, various clinical syndromes of hypogonadism have been identified, and a rational basis for therapy has been established.

Although it is possible to classify defects of the human testis in several ways, as will be evident if reference is made to the various papers cited in this article, it is reasonable on physiological and clinical bases to classify them in accordance with the time of onset of the defect and with the organ (testis or hypophysis) which is primarily at fault Thus, the syndromes may be divided into those which have their origin during the prepuberal and puberal periods and those whose onset occurs during adult (sexually matured) life. Physiologically and clinically the puberal and adult syndromes may be divided into the hypergonadotrophic (site of primary failure being the testis) and hypogonadotrophic (site of primary failure being the anterior pituitary gland) types [Nelson & Heller (5, 9)].

[1] Since the chapter on diseases of the reproductive system in Volume I of the *Annual Review of Medicine* was confined to a consideration of the female reproductive system, it is proposed in this chapter to discuss recent contributions to our understanding of diseases of the male reproductive organs An effort has been made to review as many as possible of the papers which appeared during the period January, 1945 to September, 1950 Space limitations precluded the inclusion of many papers and the discussion of all diseases of the reproductive system.

THE HYPERGONADOTROPHIC SYNDROMES

Puberal seminiferous tubule failure.—This was the first clinical entity delineated from the amorphous mass "hypogonadism" by Klinefelter, Reifenstein & Albright in 1942 (10) using the modern objective techniques of gonadotrophin assay and testicular biopsy. They emphasized the gynecomastia, azoospermia, and small testes occurring in sexually matured men The boundaries of this syndrome were soon defined by Heller & Nelson (11), who added Leydig cell failure, asssociated with moderate or severe eunuchoidism, to the syndrome.

Definition.—Puberal seminiferous tubule failure is a congenital abnormality of the testis having its origin at the time of puberty It usually involves the germinal elements primarily, but eventually the interstitial cells of Leydig also show evidence of failure.

Diagnosis.—The Leydig cell failure may not be manifest clinically at puberty, perhaps because compensatory hyperplasia of the Leydig cells enables androgen production to proceed at normal or only slightly below normal rates for some time.

Because of the variability in degree and time of onset of Leydig cell failure, Heller & Nelson (11) have described the syndrome as consisting of constant and variable features.

The constant features are (*a*) small testes (usually having harder than normal consistency and measuring approximately $1\frac{1}{2}\times1\frac{1}{2}\times1$ cm) characterized microscopically by sclerosis and hyalinization of the seminiferous tubules and by increase in numbers of Leydig cells, which usually occur in aggregated masses or clumps, (*b*) azoospermia in which ejaculation is frequently possible but the seminal fluid is devoid of spermatozoa, and (*c*) elevated urinary gonadotrophins, usually 10 to 20 times as high as in normal men.

The variable features (based upon the time and degree of Leydig cell failure) are as follows (*a*) the skeleton varies from eunuchoidal to normal, tall to short, and bone age may be grossly delayed or normal; (*b*) gynecomastia, including enlargement of nipples and areolae and palpable mammary lobules, may be marked clinically, may be undetectible upon physical examination but discovered by histological examination of breast tissue, or may be entirely absent, (*c*) the external genitalia vary from infantile to normal adult, (*d*) the hair pattern varies from sparse female to adult male, (*e*) the voice may be child-like (high pitched) or adult, (*f*) muscular development and muscular strength varies from poor to average but tends to be poor, (*g*) Leydig cell appearance may be poor or normal; (*h*) androgen or 17-ketosteroid excretion varies from low to average of normal, (*i*) estrogen excretion varies from low to average of normal

On the basis of these variable features, the syndrome has been divided into the following subdivisions: (*a*) the eunuchoidal group (least gynecomastia), (*b*) moderately eunuchoidal group, and (*c*) noneunuchoidal group (most pronounced gynecomastia). Albright and co-workers (12) agree to broadening the definition of the syndrome to include the cases without gyne-

comastia and Leydig cell failure They disagree, however, "that patients falling into this syndrome who have marked eunuchoidism are less likely to have gynecomastia than those with a more normal habitus," despite the fact that their own data [see Table 11 (12)] do not indicate this trend Instances of the syndrome have been documented by Bettinger & Robinson (13), McCullagh (14, 15), Reifenstein (16), Spankus & Grant (17), and others Reifenstein's observation of the occurrence of this syndrome in nine members of the same family (16) and those of Heller & Nelson (18) in three pairs of brothers lend support to the explanation of the syndrome on a congenital basis. Although it is scarcely possible at this time to discuss the incidence of the syndrome and its subdivisions, it may be said that the reviewers have had occasion (up to May, 1950) to examine biopsy assays and other data on 10 instances of the eunuchoidal group, 18 instances of the moderately eunuchoidal group, and 21 instances of the noneunuchoidal group as well as less extensive material on almost as many other cases believed to fall in this syndrome It seems probable that the syndrome in its several forms occurs more frequently than was originally believed to be the case.

Treatment—The gynecomastia does not respond to hormonal treatment; therefore, plastic surgery is recommended for those patients whose gynecomastia becomes s problem. The condition of hyalinization of the seminiferous tubules is, as far as is known, irreversible The majority of patients benefit greatly both objectively and subjectively from androgen administration Members of the eunuchoidal and moderately eunuchoidal variant of the syndrome usually have androgen-withdrawal symptoms during the late twenties and are candidates for treatment at that time (19) Heller & Maddock (20) recommend implantation every six to eight months of six pellets of unconjugated testosterone weighing 75 mg each.

Functional prepuberal castration syndrome—The features which distinguish this group from other eunuchoids are: absence of scrotal testes but presence of scrotal Wolffian duct derivatives, high gonadotrophins, and gross gynecomastia or, in its absence, histological evidence of departure from normal mammary development (Heller, Nelson & Roth (21)] The etiology may be congenital absence of the testes, atrophy of testes following such surgical manipulations as herniorrhaphy or orchidopexy, or spontaneous prepuberal atrophy The clinical syndrome appears to be identical with that reported by Wagenseil for prepuberal surgical castrates (22), and according to Hamilton (23), similarly high gonadotrophins are found after puberty in males castrated before puberty Other instances of this syndrome have been recorded by Fraser and co-workers (24), McCullagh (14, 15), Heller & Nelson (9), and Howard *et al* (12) In 126 cases of eunuchoidism reported by Nelson (25), 15 were diagnosed as instances of this syndrome.

Treatment consists of substitutional therapy with testosterone. The most effective and most economical way of administering this therapy is by implantation of testosterone pellets Six pellets weighing 75 mg. each are implanted subcutaneously in the mid-thigh region through a trocar This is

The Hypergonadotrophic Syndromes

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Treatment consists of substitutional therapy with testosterone. The most effective and most economical way of administering this therapy is by implantation of testosterone pellets Six pellets weighing 75 mg. each are implanted subcutaneously in the mid-thigh region through a trocar. This is

repeated every six to eight months [Heller & Maddock (20)]. The gynecomastia is not amenable to hormonal therapy. In marked instances, plastic surgery is recommended.

The "Sertoli cell only" (including germinal cell aplasia) syndrome.—Absence of germinal epithelium associated with otherwise normal seminiferous tubules discloses the naked sustentacular cells of Sertoli. This defect causes no significant deviation in the size of the testes and, since the Leydig cells are not involved, causes no aberration in secondary sexual characteristics. The only clinical symptom is sterility, manifested by azoospermia, and the only hormonal alteration is the marked increase in urinary gonadotrophins [Heller, Nelson, and co-workers (26, 27), Engle & Southam (28), and Howard *et al.* (12)]. The latter authors describe some of their cases as having normal testes and others as having "slightly small" testes. The most likely explanation for this syndrome is congenital absence of germinal cells [del Castillo, Trabucco & de la Balze (29)], but it is possible that the germinal cells are present at birth and die during relatively early postnatal life [Nelson (30)]. In some cases, the testicular biopsies show occasional tubules which do have germinal cells and varying degrees of spermatogenesis. Of 119 cases of azoospermia reported by Nelson (25), the biopsies of 46 showed germinal cell aplasia.

Whatever the etiology of this syndrome may be, it should be noted that a decrease of spermatogenic elements resulting in tubules populated exclusively or nearly exclusively by Sertoli cells is encountered in testicular defects other than germinal cell aplasia, as in puberal seminiferous tubule failure (31), cryptorchidism (12), exposure to radioactive agents (12), gonococcal and mumps orchitis (15), and idiopathic testicular degeneration (27) The end-results in such instances are similar to cases with germinal cell aplasia in that gonadotrophins are elevated and azoospermia is present. However, in these instances the testes may be smaller than normal, the peritubular connective tissues of the seminiferous tubules are almost always severely sclerosed, and completely hyalinized tubules are often encountered The condition of complete hyalinization appears to be the end-result of the increase of the peritubular tissues with death and sloughing of germinal elements. Thus, occasionally one encounters testicular biopsies in which three types of tubules are present. (*a*) those containing Sertoli cells only, (*b*) those which are completely hyalinized, and (*c*) those which are partially sclerosed or nonsclerosed and which contain germinal elements This is in contrast to the condition in the true germinal cell aplasia syndrome where the tubules present a uniform picture. Although figures are not presently available for all of the variants of the "Sertoli cell only" syndrome, it may be noted that of 119 cases of azoospermia reported by Nelson (25), 24 were instances of severe peritubular fibrosis.

Gonadotrophin assays are important in distinguishing instances of azoospermia due to block of egress of sperm and azoospermia due to germinal

cell arrest (assays normal) from the "Sertoli cell only" syndrome (assays high). Del Castillo, Trabucco & de la Balze (29) claimed that gonadotrophins are normal in all instances of the syndrome, and originally Howard, Sniffen & Simmons (32) reported that gonadotrophins were normal in approximately 50 per cent of their cases Upon reassay of some of those with normal values, the gonadotrophins were discovered to be high, and in the most recent report (12) the cases are all classified under "conditions with high FSH [follicle stimulating hormone] excretion."

The male climacteric.—There is no critical time in the life history of the human male when Leydig cell function fails, and thus no climacteric in the physiological sense, as applied to women, ensues. However, androgen withdrawal symptoms, conveniently called male climacteric symptoms, may occur as a resultant of testicular failure following gonococcal or mumps orchitis (9), cyptorchidism (12), surgical castration (23), puberal seminiferous tubule failure (19), and idiopathic Leydig cell failure. The symptoms are not unlike those of the menopause in women plus loss of libido and potentia [Heller & Myers (33), Werner, S (34), Werner, A. (35), McCullagh (15, 36).

The diagnosis is suspected from the menopause-like symptoms and may be confirmed by finding elevated gonadotrophins [Howard *et al* (12), McCullagh (15), Heller & Myers (33)]. Testicular biopsies, according to Nelson & Heller (5) and Heller & Myers (33), reveal deviations in Leydig cell morphology although Howard *et al.* (12) were unable to recognize Leydig cell defects in biopsies of six cases.

In lieu of biopsies and gonadotrophin studies, Heller & Maddock (20) have suggested a therapeutic test using testosterone propionate. Twenty-five mg. of testosterone propionate are administered intramuscularly daily for two weeks, and the patient is interviewed at the end of the 3rd week. The test is considered positive for the male climacteric if gradual improvement and gradual relapse occur. The test is considered negative if no benefit occurs or if prompt relief and prompt return of symptoms is noted

Treatment—In three of the types of hypogonadism discussed above (puberal seminiferous tubule failure, functional prepuberal castration, and the male climacteric), substitution therapy with androgen is advised Three forms of therapy are currently used. daily injections of 25 mg of testosterone propionate, 10 to 50 mg of testosterone propionate (19) or methyl testosterone administered sublingually [Lisser (37)], or implantation of six or seven pellets of unconjugated testosterone propionate. This latter treatment should be repeated after six to eight months and probably is the most economical and convenient form of therapy which is presently available.

The Hypogonadotrophic Syndromes

Hypogonadotrophic eunuchoidism.—Eunuchoidism due to secondary testicular failure may be suspected clinically from the finding of scrotal testes which, on palpation, are in no way different from those of a normal prepu-

beral boy and from the absence of gynecomastia (either grossly or microscopically). The diagnosis is confirmed by the failure to find gonadotrophins in the urine and by testicular biopsy which reveals prepuberal testes [Heller & Nelson (9, 26), McCullagh (14, 15), Fraser *et al.* (24), Howard *et al* (12)] The syndrome is the resultant of failure of secretion of pituitary gonadotrophins at the expected time of puberty and may be regarded as indefinitely delayed adolescence. Indeed, examples of the condition have been observed in men over 60 years of age.

Stimulatory therapy with gonadotrophins is indicated. Optimal treatment consists of administering 1,000 I.U. of chorionic gonadotrophin intramuscularly twice daily. More convenient and equally effective is the intramuscular injection of 5,000 I.U. of aqueous chorionic gonadotrophin three times weekly (38). Since chorionic gonadotrophins are derived from human pregnancy urine, antihormones are not formed Thus, the serum of patients who have received as much as 1.5 million units over a three year period did not show antigonadotrophic agents (39). Rest periods of at least six months are provided after maturation is well advanced, usually in 6 to 18 months During the rest periods, the patient's condition may regress, remain stationary, or maturation may progress. The latter result is common. Treatment in some unknown manner appears to stimulate the pituitary gland with the result that maturation continues spontaneously and further treatment becomes unnecessary.

Adult hypogonadism secondary to pituitary failure.—Extensive observations by McCullagh, Gold & McKendry (40) reveal that pituitary lesions are often followed by disappearance of gonadotrophins from the urine and a reversal of testicular morphology to a nearly preadolescent state The Leydig cell failure may be corrected by administration of chorionic gonadotrophins. Correction of the pituitary involvement by removal of the tumor may lead to correction of both the germinal and hormonal defects of the testes.

Secondary testicular failure in paraplegia —Lesions of the spinal cord may result in loss of potentia, infertility, and gynecomastia [Cooper & Hoen (41), Horne, Paull & Munro (42, 43]). The testicular biopsy generally reveals [illegible]

Male infertility.—With the advent of the technique of testicular biopsy, it has been possible to recognize and classify the various testicular and re- [illegible]

has been possible to recognize four types of testicular defects· (*a*) normal or essentially normal spermatogenesis [in these cases it can be shown that the efferent ducts are occluded or absent; this condition was observed in 22 of 119 men whose seminal specimens lacked sperm (25)], (*b*) germinal cell arrest (this condition, observed in 27 of 119 cases, is one in which spermato-

genesis fails to progress beyond one of the immature stages, usually the primary spermatocyte), and (c) generalized peritubular fibrosis (24 of 119 cases) and germinal cell aplasia (46 of 119 cases) which have been discussed under the heading of the "*Sertoli cell only*" *syndromes*.

Infertile men whose seminal specimens contain less than the usual normal numbers of sperm (more than 60 million per ml) or in which unusual numbers of abnormally formed sperm are found are likely to have testes in which the following conditions can be recognized: (a) disorganization of spermatogenesis with sloughing of immature forms, the most common defect [observed in 152 of 378 men with oligospermia and/or unusually high percentages of abnormal sperm (25)], (b) incomplete germinal cell arrest, similar to the condition of germinal cell arrest in azoospermic men, but involving less of the spermatogenic elements (74 of 378 cases), (c) regional peritubular fibrosis, similar to this condition in azoospermic men but less extensive (58 of 378 cases), (d) germinal cell atrophy or hypoplasia due to failure of spermatogonia to maintain a normal production of germ cells (30 of 378 cases), and (e) abnormal chromosomal and mitotic activity of germ cells (64 of 378 cases)

In the azoospermic group, men with normal testicular morphology may be restored to fertility by successful anastomoses of the obstructed efferent ducts (2) No treatment can be offered men with germinal cell aplasia and probably the same is true of most, if not all, men with generalized peritubular fibrosis (However, in the latter case see p 186) In azoospermic men with germinal cell arrest and in oligospermic men with the various types of defects which have been noted, the outlook is more hopeful, according to recent observations, although it is unlikely that the spermatogenic activity of the testes can be improved in all instances by the methods available at the present time There is reason to suspect that, in many men, the germ cells are constitutionally defective, particularly in the cases of germinal cell arrest and abnormal chromosomal and mitotic patterns [Engle (46), Nelson (25)] In these groups, it is unlikely that present methods will achieve success in the majority of cases

However, correlation of the findings of testicular biopsies and gonadotrophin assays has led to two suggestions for the hormonal treatment of defective spermatogenesis. These should be adopted only after the patient has been studied thoroughly and various extragenital causes of infertility eliminated or corrected as suggested by Hotchkiss (2)

In cases of oligospermia associated with testicular pictures of premature sloughing of germ cells and relatively mild disorganization, Heller (47) has indicated that the use of gonadotrophin may improve spermatogenesis Other *conditions which may respond to such treatment are germinal cell* arrest (but see p 182) in men with azoospermia and oligospermia and in cases of germinal cell atrophy or hypoplasia. It should be noted that in these cases the urinary levels of gonadotrophin are low or normal

In men whose testicular defects are considered to be severe disorganiza-

tion of the spermatogenic process and premature sloughing of germ cells or severe, but not complete, peritubular fibrosis, administration of testosterone appears to offer encouraging results (50). It will be noted that, in these men, the urinary levels of gonadotrophins are usually elevated.

Gonadotrophin therapy is complicated by the formation of antihormones. Maddock (48) has demonstrated that antihormone formation occurs about six weeks after initiating pituitary gonadotrophin therapy. Jungck *et al* (49) further clarified the situation by finding that the antihormones to exogenously administered pituitary hormone, in the form of extracts of pituitary glands, acted against the patient's own pituitary gonadotrophism with the result that the testes became atrophic and sperm counts fell below pretreatment levels. The use of pregnant mare serum (PMS) gonadotrophin, while limited to six weeks of usefulness when given intramuscularly in doses of 1,000 I.U. daily because of antihormone formation, is advocated because no effect against the patient's own gonadotrophins occurs. Sperm counts continue to rise for some months after treatment when PMS is discontinued (47).

The effect of administering 25 mg. of testosterone propionate daily for 60 to 90 days is to decrease spermatogenesis initially (usually to zero activity), accelerate peritubular fibrosis, and to cause disappearance of Leydig cells. Remarkable recovery begins about six months after discontinuing treatment and is complete 18 months afterwards. At this time, testicular histology is frequently indistinguishable from normal, and sperm production is normal as reported by Heller and co-workers (50, 51) This rather extraordinary observation, which has no entirely satisfactory explanation, has been confirmed by several workers (52) who have applied the procedure in patients with oligospermia.

Cryptorchidism

Probably the most comprehensive recent review of this subject has been written by Bishop (53) He points out that the incidence of undescended testes is 10 per cent at birth, 2 per cent at puberty, and 0 2 per cent in adult life. Thus, spontaneous descent does occur in the vast majority of individuals who are cryptorchid at birth, and because of this fact, many pediatricians and urologists prefer to withhold medical or surgical intervention until the early puberal years have been attained This policy of watchful waiting would be indicated if it could be assured that the undescended testis does not suffer during 12 to 15 years of exposure to elevated temperatures as had been more or less tacitly assumed by many people However, if damage does occur during this period of retention, the testes of a considerable number of males may undergo changes which interfere with fertility in later life. Indeed, a note of warning in this regard was sounded by Cooper (54), who reported that the undescended testis does undergo damage during the prepuberal period. This observation was confirmed recently b~ Nelson (55) on the basis of observations on both rat and human testes H

that the decline in the number of germinal cells in undescended testes may be due frequently to congenital inferiority of such gonads rather than to the effects of elevated temperature.

The question as to the relative value, in the treatment of cryptorchidism, of surgical procedures and endocrine treatment (androgenic hormone and/or chorionic gonadotrophin) has remained controversial. Frequently, too little regard has been given to the position of the undescended testes and the nature of the factors which promote or interfere with their descent. Wells & State (56, 57) have analyzed this subject, as has Bishop (53) Further confusion exists because of the lack of sufficient attention to the eventual success of the procedures Many surgeons have regarded the index of success to be placement of the testis in the scrotum, although considerable trauma to the testis and the blood vessels may have ensued during surgical manipulation (58) The only true index of success should, of course, be demonstrated fertility. Hansen (59) has carried out the type of study which must be done before one is in a position to evaluate both the methods of treatment and the age at which treatment should be instituted In a study of 73 men who had been treated for undescended testes by orchidopexy and 42 unilaterally cryptorchid men who had received no treatment, Hansen came to the conclusion that very few testes which were placed in the scrotum by surgical procedures produced spermatozoa in sufficient numbers to permit fertility In this and in a second paper (60), Hansen decries the use of surgery until treatment with chorionic gonadotrophin has been given an adequate trial. He also makes a plea for extensive follow-up studies, and with these points Bishop concurs. Such follow-up studies for medical as well as surgical procedures in cryptorchidism have been neglected. Those which seem to have been made, except for that of Hansen, have either not been continued for a sufficiently long period of time after treatment or have not been sufficiently critical to offer satisfactory information [Kafka (61), Lapin *et al* (62)].

In evaluating the results of treatment of the undescended testis, it should be borne in mind that ectopia of the testis may be, in many cases, only one evidence of its defective development and that poor fertility following any form of treatment may be expected This idea was expressed first by John Hunter in 1839 and has been emphasized by others more recently (55). The relatively frequent observation that cryptorchidism occurs in brothers [Brimblecombe (63)] lends support to this point of view

For many years, it has been rather generally assumed that the undescended testis secretes normal quantities of androgenic hormone and that the Leydig cells undergo hyperplasia as the seminiferous tubules atrophy [Moore (64)] However, Hanes & Hooker (65), Nelson (66), and Pace & Cabot (67) have presented evidence to the contrary Recently, Engberg (68) has made a study of the hormone excretion of cryptorchid men, and he reports that androgen excretion is decreased, the estrogen output remains essentially the same as in normal men, and the excretion of gonadotrophin is increased

Pubescence in the Male

Some of the disorders which relate to disturbances of puberty have been discussed in early sections of this review (puberal seminiferous tubules failure, prepuberal functional castration, hypogonadotrophic eunuchoidism) Several significant contributions have been made to subjects relating to the phenomena and the normal limits of male pubescence and to the management of normal and disturbed puberty. Among them are papers by Schonfeld (69, 70, 71) and Greulich *et al* (72) on questions involving normal variations in growth and sexual maturation during puberty and adolescence and the management of that period, and summaries by Hurxthal (73) and Wilkins (74) of the types of hypogenitalism which are encountered during the usual period of puberty.

Mumps Orchitis

The importance of mumps orchitis as a causative factor in male sterility probably has been exaggerated. In the various studies which have been made on infertile males in recent years, very few cases have been encountered in which a history of the disease could be elicited It has been estimated that only 3 per cent of all cases of mumps develop bilateral mumps orchitis [Wesselhoeft (75)] and that the incidence of sterility due to mumps orchitis is 1 in 175,000 However, the subject has received recent attention, and two interesting papers have appeared on the histopathology of the disease [Gall (76), Charny (77)] These papers were based on biopsy tissue secured during the early and subsequent stages of the infection and showed the presence of early transient edema followed quickly by inflammatory cell infiltration, destruction of germ cells, and peritubular fibrosis. Most, if not all, of the tubules which are affected by the process are so seriously damaged as to render recovery impossible. From these studies, it would seem probable that the practice of incising the testicular capsule would be of little value after the first day of the disease The surgical treatment of mumps orchitis has been reviewed recently by Nixon & Lewis (78) Rambor (79) has discussed the use of convalescent serum in the treatment and prophylaxis of the disease, and Savran (80) has described the use of estrogenic hormone. It is somewhat difficult to explain the manner in which the latter treatment protects the testis from orchitis, since estrogens have been shown on many occasions to cause testicular damage due to inhibition of pituitary gonadotrophins Perhaps the [illegible] action [illegible] ally [illegible] ary inhibition of the pituitary gonadotrophins by the administration of estrogen would in effect tend to return the testis to its perpuberal status. Further studies on the use of estrogens and the mechanism whereby protection is afforded are necessary.

Testicular Tumors

Numerous papers relating to various aspects of neoplasms of the testis have appeared in recent years, but the subject has continued to present a generally confused state. This stems principally from the lack of agreement on classification of the tumors and on the interpretation and significance of assays for gonadotrophic hormone in the urine of patients with testicular tumors

Probably the most comprehensive paper, and one which should provide a basis for clarifying the confusing issues of classification and tumor relationships, is that of Friedman & Moore (81). They reviewed 922 cases of testicular tumors, presented a reasonable and relatively simple scheme of classification, and suggested a basis for the interpretation of the origin and relationship of these neoplasms. Others who have reviewed fairly large series of cases are Lewis (82) 250 cases, Kelby & Stenstrom (83) 100 cases, and Nesbit & Lynn (84) 80 cases A perusal of these and other similar, but less extensive, series will impress the reader with the generally chaotic state of the subject Perhaps one of the most disturbing observations is the frequency with which metastatic growths reveal distinct morphological differences from the type of tumors suggested by the pathological report on the primary growths However, as various authors have emphasized, a primary growth may show quite different conditions in its various areas, and unless many blocks are sectioned, the complete picture cannot be obtained Furthermore, if Friedman & Moore are correct in their interpretation of the etiology of testicular tumors, the tumor cell, being a very primitive element, possesses the potentiality for differentiating into other types of the generally recognized testicular tumors. This is specifically true of the embryonal carcinomatous cell which may differentiate into the syncytial and Langhans cells of the chorioepitheliomata or into the adult tissues of the teratomata The so-called seminomas (probably better termed dysgerminomas), on the other hand, probably do not possess this capacity for differentiation, and the finding of chorionic elements in their metastases may be taken to indicate the unrecognized presence of such elements or of embryonal carcinoma in the primary growths Indeed, as Friedman & Moore (81) and Twombly (85) have shown, these mixed tumors do occur in the same testis.

The status of assays of urine for gonadotrophic hormone is equally unsatisfactory, although most of the existing confusion seems to be unnecessary and due primarily to a lack of understanding of the nature of the hormones which are present in men with testicular tumors. When Ferguson (86) published his findings on the amount of gonadotrophin excreted in patients with various types of testicular tumors and the effect of treatment upon the levels of gonadotrophin, it was optimistically believed that not only could the type of tumor be diagnosed, but also that the prognosis of individual cases might be determined by use of the method. However, the results obtained by many

Pubescence in the Male

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called Sertoli cell tumors These are very rare; indeed, it is uncertain that the latter type actually occurs in man, and some of the tumors identified as being of interstitial cell origin may have been incorrectly diagnosed.

Melicow and co-workers (95) reviewed the cases reported in the literature through 1947 and found 36 cases of interstitial cell tumors, nine of them in children. To this list, they added a case of their own which occurred in a 5½ year old boy. Four other tumors which probably are interstitial cell adenomas have been reported more recently, one each in boys by James & Shupe (96) and Sanborn (97) and two in adult men by Reiners & Horn (98).

The physiologic effects of interstitial cell tumors are most evident when they occur in prepuberal boys, in whom they induce precocious growth and sexual maturation. In adult men, there is little evidence of endocrine disturbance except for the occasional occurrence of gynecomastia Only five of the tumors appear to have been malignant.

The difficulty which has been encountered in classifying tumors which appear to have arisen from interstitial cells stems largely from the frequent resemblance of the tumor cells to cells of the adrenal cortex. As a result, suspicion arises that at least some of these tumors develop from aberrant adrenal cells. For example, two cases reported recently were classified as being of such origin [Ostergaard (99), Cohen (100)] This is understandable since, as Wilkins (74) has recorded, 12 cases of adrenal tumors which were associated with gynecomastia have been observed Furthermore, the proximity of gonads and adrenal cortex during development provides a reasonable basis for presuming that dislocations of primitive adrenal cells to the gonads may occur. However, cognizance should be taken of the fact that young Leydig cells resemble the zona reticularis cells of the adrenal more closely than they do the usual concept of a Leydig cell.

The interesting suggestion that the Sertoli cell forms tumors which are feminizing through the production of estrogenic hormone was made by Huggins & Moulder (101) as a result of a study on feminized male dogs Such tumors have not been identified with certainty in man, although Teilum (102) has reported a case which he believes to be of Sertoli cell origin Teilum, in other papers, developed the idea that the Sertoli cells produce estrogen (103) and that the tumor reported by him is homologous with certain granulosa cell tumors (104) For this group of tumors he proposed the term "androblastoma tubulare lipoides." Lewis & Stockard (105) have recently reported a tumor in a 68-year-old man which they believe to be similar to Teilum's case, although the morphological similarity cannot be detected from the published photomicrographs The interesting feature of their case was the observation that, although the excretion of estrogen was recorded as not having increased, significant amounts of pregnanediol were found. The only other cases of testicular tumor in which the excretion of pregnanediol seems to have been noted were two men with chorionepithelioma (85, 111).

The idea that the Sertoli cells not only give rise to tumors which produce

workers were so divergent that in recent years less and less attention has been paid to the study of gonadotrophins as either a diagnostic or a prognostic measure. Most of these observers have failed, apparently, to take into account certain fundamental facts concerning the nature of the gonadotrophic hormones and have followed Ferguson's original assumption that only one gonadotrophin, chorionic gonadotrophin, occurred in the urine of men with testicular tumors This assumption has persisted in many quarters, although as long ago as 1933 Hamburger (87) showed that such urines contained not only chorionic gonadotrophin, but also a pituitary gonadotrophin (FSH), and he has described procedures for clearly differentiating these hormones (88). Thus, he has reported that men with tumors usually classified as seminomas and adult teratomas frequently excrete pituitary FSH, although in occasional cases chorionic gonadotrophin also may be found. These may be instances of mixed tumors. On the other hand, chorionepitheliomas and embryonal carcinomas are associated with the excretion of chorionic gonadotrophin. This latter hormone is produced by chorionic elements (Langhans cells) or their presumed precursors, the more primitive embryonal carcinoma cells, while pituitary FSH is supposed by Hamburger to be produced in excessive amounts by the patient's pituitary when the lesion interferes with the androgen production of the testis and/or following removal of the testis with its lesion. In a separate paper, Hamburger & Godtfredsen (89) reported that the androgen production of men with seminomas is reduced to the level of castrates Although they do not uniformly support all of Hamburger's interpretations, Twombly (85), Vermooten & Hettler (90), Sorba (91), and Laqueur (92) are in substantial agreement with his thesis It would seem advisable for anyone attempting hormonal assays in men with testicular tumors to familiarize himself with the distinctions between pituitary and chorionic gonadotrophins

It now appears to have been clearly shown that an undescended testis is much more likely to be the site of a testicular tumor than a scrotal testis [Bishop (53), Lewis (82), Gilbert & Hamilton (93)]. Although estimates vary, it would appear that about 11 per cent of all testicular tumors arise in undescended testes and that the correlation of tumor and faulty descent is approximately 48 times greater than would be expected on the basis of chance association. The most common type of neoplasm appears to be the seminoma, and according to Gilbert (94) and Lewis (82), orchidopexy does not improve the chances of an undescended testis to escape neoplastic involvement This observation might argue for the surgical removal of all undescended testes, except for the fact that, even in such testes, the incidence of cancer is relatively low. The observation does emphasize the point which was made in an earlier section (p. 187) regarding the possibility that many undescended testes are congenitally defective organs

Recent observations on two types of testicular tumor which usually are benign deserve mention These are the interstitial cell tumors and the so-

(116, 117), Hibbs (118), Jacobs (119), Platt *et al* (120)] are in substantial agreement. Approximately 10 per cent of the prisoners developed gynecomastia, the majority after institution of an improved nutritional status. Here, as in the gynecomastia associated with hepatic cirrhosis and other diseases which provoke a state of poor nutrition it is believed that damage to the liver occurs to the extent that it interferes with its capacity to conjugate or destroy estrogens. As a consequence, larger amounts of free estrogen are available to stimulate the susceptible tissue of the breast Coodley & Molle (121) studied the excretion of estrin in a cirrhotic and found that, as the nutritional status and the condition of the liver improved, the excretion of both free and total estrogen was reduced, indicating increased destruction of estrogen by the liver.

Seven cases of gynecomastia in paraplegic men were reported by Cooper & Hoen (122). The testes of these men were said to be within low normal limits in size, but no biopsies were obtained nor were hormone assays made On the other hand Bors and co-workers (123) reported that of 34 paraplegic men only three showed normal testicular histology Urinary 17-ketosteroid levels were normal; gonadotrophin levels were low in 25 of the 29 tested; and estrogen levels were high in 30 of the 34 patients Although these authors made no mention of gynecomastia in their patients, it would seem likely that they may have provided the answer for the presence of gynecomastia in the patients of Cooper & Hoen. Cooper *et al* (124) described gynecomastia in two patients with disease of the spinal cord (a 21-year-old man with atypical Friedreich's ataxia and a 45-year-old man with syringomyelia). In the first case, the testes were atrophic Hormone studies showed low urinary levels for 17-ketosteroids and gonadotrophins and low normal levels of estrogen. In consideration of the findings in these cases and of related observations in other types of lesions of the spinal cord, these authors are inclined to favor the idea that gynecomastia and hypogonadism occur secondarily to lesions of the cord.

Although an explanation which will account for the various instances of gynecomastia cannot be provided at this time, enough evidence is at hand to indicate the intimate participation of estrogenic hormone However, as a consideration of the evidence will show, some other factor or factors must be involved It is possible that the recent demonstration by Lyons (125) that prolactin plays an important role in the growth of the breast and that placental tissue is a rich source of that hormone will provide us with a better basis for understanding the occurrence of gynecomastia

PROSTATE

Prostatic Hypertrophy

This condition is common in men past the age of 60 [according to Heckel (126), 55 per cent, and to Carroll, (127) 35 per cent] Although surgical resection continues to be the treatment of choice for benign hypertrophy of the

estrogen (and perhaps progesterone) but also produce estrogen under normal circumstances is intriguing, but would appear to require more direct evidence than has been offered. At the present time, it is possible to make an equally attractive case for the Leydig cell.

GYNECOMASTIA

Karsner (106) has provided a recent comprehensive paper on the subject of hypertrophy and hyperplasia of the male breast based on the study of army personnel and including a consideration of nutritional, hormonal, and disease factors. He states that the incidence of gynecomastia in the groups under consideration was 16 per 100,000 men.

As Jung & Shafton (107) have shown, growth of the breast is an integral part of the puberal process in boys as well as girls. Usually it is transient, but in some otherwise normal boys, this puberal gynecomastia is retained. The frequency of unusual breast development is even more common in some types of hypogonadism (8, 11, 21) where it tends to persist. The administration of testosterone in eunuchs has been noted by McCullagh & Rosmiller (108) to be followed by transient gynecomastia. As Nathanson (109) has indicated, a form of gynecomastia is encountered in old men, and furthermore, this epoch of life as well as that of puberty is one during which changes in the levels of androgen and estrogen occur.

Gynecomastia has been observed frequently in men with testicular tumors, particularly those which contain, or are believed to contain, chorionic syncytial elements [Gilbert (110)]. The latter are considered to be the cells which produce estrogen in the normal placenta, and it is probable that they also produce estrogen when they occur in testicular cancer. Gynecomastia has also been observed in men with interstitial cell tumors and was seen in the cases of Ostergaard (99), Teilum (102), and Lewis & Stockard (105). Unusual growth of the male breast occurs in cases of chorionepithelioma which arise extragenitally [Laipply & Shipley (111), Caes & Cragg (112)]. In such cases the high levels of estrogen stimulate breast growth, while the testes usually show atrophy and hyalinization of the tubules and interstitial cell hyperplasia The latter effect is due to the large amounts of chorionic gonadotrophin which is produced by the tumor and its metastases. The reviewers (113) have had occasion to see three of these cases, in each of which the primary site was the anterior mediastinum. Of particular interest was the occurrence of such a tumor in an 11-year-old boy He underwent a period of rapid growth and sexual maturation before death due to pulmonary metastases. Gynecomastia was present and the testes, although small, showed widespread interstitial cell hyperplasia

Numerous papers have appeared on the subject of gynecomastia in men with disturbed nutritional states These include accounts of gynecomastia in men with hepatic cirrhosis [Lloyd & Williams (114), Mithoefer & Bean (115)] and various discussions of the occurrence of breast hypertrophy in soldiers who had been confined in prison camps The various reports [Salter *et al*

Brendler (133) noted that some patients with extensive metastases who failed to gain relief with estrogens did show clinical improvement when treated with androgenic hormone. This observation, reminiscent of the observations in carcinoma of the breast, emphasizes the need for more detailed studies on the entire subject of the effects of hormones upon metabolic processes in relation to the growth of cancer cells.

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prostate gland, publications suggesting the use of androgens or estrogens and of castration have continued to appear These procedures are considered by Farman (128), Carroll (127), and Heckel (126). Although urinary symptoms may be relieved in some cases by either androgens or estrogens, the relief is only temporary, and the size of the enlarged gland is not materially affected The rationale of treatment with these hormones is based upon animal studies in which it has been shown that androgens will induce prostatic enlargement and others in which estrogen has in some animals caused hyperplasia of certain prostatic elements These studies are not readily adapted to hypertrophy of the human prostate since the latter does not involve the same histologic alterations which are seen in the studies on animals. However, the attractive theory that prostatic hypertrophy is a consequence of disturbed androgen-estrogen ratios has served as a basis for therapeutic use of one or the other of these substances On the other hand, there is better agreement on the beneficial effects of either androgens or estrogens in the treatment of prostatitis, and Heckel (126) advocates the use of estrogen in cases of premature ejaculation and hematospermia.

Prostatic Cancer

Although the fundamental studies of Huggins and his colleagues (129) on the effects of castration on prostatic cancer have continued to receive widespread application in the treatment of that disease, there appear to have been no important advances in the subject during the past few years Opinion has remained divided upon the relative efficacy of surgical castration and physiological castration by treatment with estrogenic substances, upon the order in which the two procedures should be employed, upon the extent in which primary and secondary growths are effected, and upon the doses of estrogen (usually diethylstilbestrol) which should be administered [Heckel (126), Huggins (129), Herger & Sauer (130), Flocks (131)].

In general terms, it may be said that either surgical or physiological castration will result in the improvement of most patients with carcinoma of the prostate In some cases, the combination of castration and treatment with diethystilbestrol in series provides for prolongation of the initial relief The most common and lasting benefit which has been observed is relief of pain and generally improved physical condition Decrease in size of the original tumor and its metastases are frequently noted, but for only a relatively short time in the majority of cases Although improvement may persist from a few months to more than five years, cures cannot be expected Flocks (131) recommends doses of diethylstilbestrol up to several hundred milligrams daily in cases where metastatic bone pain remains intractable to the usual 1 to 5 mg doses, and he indicates that this treatment appears to relieve the pain although not the enlargement of the breasts, which undergo hypertrophy during treatment with estrogens Although Huggins (132) has reported that androgenic hormone strikingly increases the growth of prostatic cancer,

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DISEASES OF THE NERVOUS SYSTEM[1]

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Polyneuritis and Neuronitis

During 1949 to 1950, a revolutionary new understanding of the chemical mechanism of polyneuritis has crystallized from the original work of Peters in the development of BAL (2,3-dimercaptopropanol) used successfully to counteract lewisite poisoning. Hughes (1) has given an excellent summary of the reasoning and work of Peters, which has led to the concept that nearly all, if not all, polyneuritis is an enzyme disease.

Peters found that convulsions occurring in cases of thiamine deficiency resulted from a break-down of the pyruvate-oxidase system, which included thiamine. The diseased enzyme in such deficiency was shown to be thiamine pyrophosphate linked with a sulfur-containing protein It was also shown that this enzyme, which was essential to physiological activity of neurons, could be inactivated not only on the carbohydrate side through lack of thiamine, but could be poisoned separately on the protein side, especially by iodoacetic acid Thiamine was, therefore, one essential to healthy neurons, but not the only one. This simple fact explains why it is useless to continue with enormous doses of thiamine when the patient with polyneuritis does not respond.

Peters next observed that iodoacetic acid, the known poison for the protein moiety of the enzyme, was a mild epithelial vesicant, and he noted that it had the vesicant factor in common with lewisite, an arsenic-containing poison. By further experimentation, he then showed that lewisite acted through its arsenic and that the mechanism was based on its avidity for the sulfhydryl (SH) radical of the protein moiety of the pyruvate-oxidase enzyme system He instituted a search for a sulfur-containing compound which would compete with the protein for the available arsenic. The dithiol, 2,3-dimercaptopropanol, commonly called BAL for British Anti-Lewisite, was found to be most effective. It has now been given the U S.P. name of dimercaprol; its formula is



Through much excellent clinical and biochemical experimentation, it was gradually discovered that gold, lead, cadmium, mercury, and heavy metals in general caused polyneuritis by the same mechanism as did arsenic,

[1] This review covers approximately the period from April, 1949 to June, 1950

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Further evidence of similarity is found in Wolinetz & Dessevedavy's case of successful nicotinic acid treatment of a porphyric syndrome (7). It is probable that vitamin B_{12} will also be of benefit.

The net result of all this work is the implication that toxins affecting motor neurons act to cause paralysis through poisoning of the neuronal cellular enzyme systems. The sensory neurons are probably not affected in the same way as motor neurons, as is evidenced by total lack of response of sensory polyneuritis to BAL and their extreme refractoriness to thiamine and nicotinic acid. The next year can be expected to reveal further progress.

Integration within the Spinal Cord and Chordotomy

When Sherrington's classic work on the integration within the spinal cords of dogs was reported, the general neurological profession felt that the application of such knowledge to the human being was impossible. A dog with severed cervical spinal cord would scratch an irritated spot on the shoulder with a hind foot How could the hind leg "know" where to scratch, and how was it guided even if it "knew"? Now the results of surgery for parkinsonian tremor and for athetosis by section of tracts in the spinal cord call for a re-evaluation of the old question Ebin (11), Putnam & Herz (12), Oliver (13), and others have made sections which 20 years ago would have been considered permanently disabling lesions; yet, the patients, though weak, are able to walk about

In general, this type of chordotomy is called pyramidotomy, but it is agreed by all that more than the pyramidal tracts are severed. Ebin has even sectioned both right and left pyramidal tracts for bilateral tremor, and the patients were not completely paralyzed These demonstrated facts must cause us to modify our former concepts There must be many shunts both centrifugally and centripetally within the spinal cord. The pyramidal tracts are not the only motor pathway from the brain or in the cord, and the tracts conveying sense of touch must be not only diffuse but capable of roundabout pathways as they ascend This is a fertile field for further study, as there are many unknown factors While the tremor of parkinsonism is relieved, the rigidity is not, and associated automatic movements are not restored by the operations

Multiple Sclerosis

The Association for Research in Nervous and Mental Disease met in New York in December, 1948, and the papers presented appeared in print in 1950 (76) One feature of this work stands out clearly. It is necessary to distinguish between etiology and mechanisms. The great majority of the papers in the symposium concern themselves with the mechanisms by which the etiology produces its pathological anatomy and, therefore, its symptoms. The treatment so far available is designed to prevent the mechanism and in no way attacks the primary etiology.

Geographic distribution.—Limburg (14) made a study of the geographic distribution of multiple sclerosis and estimated its prevalence in the United

but that in some instances, BAL was not practical. It would cause lead to disappear from the circulation, but not from the body. It would unite with cadmium to form a substance more toxic than cadmium itself. On the other hand, it would save lives in cases of mercurial poisoning and would alleviate the symptoms of gold poisoning.

On the assumption that polyneuritis of unknown origin might also respond to BAL, Nielsen instigated Furmanski to study its effect on such cases. Furmanski (73) found it curative or beneficial in a small series of cases. He was then asked to try it on cases of neuronitis and again found it beneficial. While further work was being done in that field, Hughes (1) suggested that the hypothesis of a "biochemical lesion" might be extended from polyneuritis to include the possibility of lesions by heavy metals in systems other than the pyruvate-oxidase system.

That BAL is not the entire answer to polyneuritis and neuronitis is indicated by Nielsen (2), who reported on 10 cases of the Guillain-Barré syndrome of "polyneuritis with facial diplegia," of "neuronitis" with albumino-cytologic dissociation in the spinal fluid, and other neuronitides. In some cases, the syndrome was only temporarily relieved; in others not relieved at all. When the syndrome was due to diphtheria, benefit was obtained, but when due to diabetes, BAL was of no assistance. Reitman & Rothschild (3), in discussing polyneuritis with facial diplegia, suggest that the albuminocytologic dissociation found in the Guillain-Barré syndrome depends on constriction of the nerve roots by the meninges and not on the etiologic agent.

Stearns (4) has presented a survey of the pathology, etiology, and clinical material under designations such as infectious polyneuritis, neuronitis, or Guillain-Barré syndrome It is clear that the last-named syndrome is purely descriptive and not any more specific in its field than are Ménière's syndrome and Landry's paralysis in theirs. The Guillain-Barré syndrome has been known to result from anti-rabies vaccine [D'Ingianni & Fontenelle (5)], from infection responding to penicillin therapy [Morandini (6)], porphyria [Wolinetz & Dessevedavy (7)], and probably gold poisoning [Stefanini & Montanari (8)]. The pathology has been variously reported by Laruelle & Reumont (9) and by Scheinker (10) Scheinker, in 10 cases, found a pronounced and widespread swelling of the nerve fibers of the spinal cord roots and tracts and of the cranial and peripheral nerves

It has been evident for some time that there must be a common factor in the modus operandi among thiamine deficiency, pellagra, SH radical intoxication susceptible to treatment with BAL, and porphyria The well-known polyneuritis with involvement of bulbar musculature and vegetative fibers in porphyria resembles poliomyelitis and polyneuritis. The sensitivity to light in cases of congenital porphyria resembles the sensitivity of pellagrines. Moreover, cases of "Landry's paralysis" have shown porphyria. The obvious implication is that cases of porphyric polyneuritis should now be treated with BAL experimentally. Hughes (74) has tried it with good results in one case of pellagrinous polyneuritis with sensitivity to light.

5. There is not the remotest reason for considering multiple sclerosis a psychogenic disease The most that can be said is that emotional factors may be of importance in provoking attacks, or in abetting regression

Mackay (29) concludes his studies on the familial occurrence of multiple sclerosis with the following:

The following theory is consistent with our present information:
(a) There is a familial, constitutional "Bereitschaft," or *vulnerability* to multiple sclerosis This vulnerability, possibly nonessential and nonspecific, is subclinical, and *per se* inadequate to produce the disease (b) There is a second, nonfamilial, probably exogenous cause or group of causes, which is competent to evoke the disease, especially when the first, or constitutional, factor is already present.

Again with regard to mechanisms, Grain & Jahsman (23) found abnormalities of peripheral circulation in a high percentage of cases of multiple sclerosis, the most characteristic abnormality being spasm of the peripheral capillaries and arterioles. They believe, however, that the prime importance of angiospasm in the etiology of multiple sclerosis has not been established; its occurrence is merely a useful diagnostic sign.

Keschner (27) studied the effects of injuries and illnesses on the course of multiple sclerosis These are frequently matters of great medicolegal importance. His conclusions are as follows:

(1) A severe trauma to the head or spinal column may aggravate the course of multiple sclerosis (2) Infections, especially of the throat and sinuses, and pregnancy and parturition may have a similar effect (3) Associated illnesses, other than infections, have no effect on the course of multiple sclerosis (4) Operative procedures, by themselves, have no effect on the course of multiple sclerosis, but when the operative procedure is to be performed under anesthesia, general anesthesia is preferable to spinal anesthesia. (5) Pregnancy and parturition may aggravate the course of multiple sclerosis (6) Abnormal mental states have no effect upon the organic neurological picture of multiple sclerosis, but an aggravation of the latter may have an adverse effect on the abnormal mental state (7) There is no particular mental disorder characteristic of multiple sclerosis (8) In view of the great frequency of spontaneous remissions and exacerbations in multiple sclerosis it may in some cases be impossible to state with reasonable certainty whether an exacerbation following infection, injury, pregnancy and parturition or some intercurrent illness is actually the result of any of these conditions, or whether it is a fortuitous incident that would probably occur in normal distribution curves for a large group of patients with any other type of chronic progressive illness

Tillman (28) studied the effect of pregnancy The well known tendency of pregnancy to cause exacerbation of multiple sclerosis, either during or after, was emphasized and the questions of therapeutic abortion and management of pregnancy discussed There is no general rule, but each case should be handled on its own merits State laws determine what is to be done in many instances and do not allow the physician to use his judgment.

Pathology of multiple sclerosis.—The age-long discussion concerning the question of whether multiple sclerosis is primarily infectious and, therefore,

States. The lucid fact emerges that the disease occurs in colder climates in greater degree than it does in warmer climates. A map of the United States shows that where deaths of multiple sclerosis were greater than 1.2 per 100,000, the distribution was represented by a horizontal line midway between the Gulf of Mexico and Canada, with the northern half in the group of larger number of deaths. This fact has previously been found in Europe, and it is striking in Italy, in that in the northern mountainous region there, a higher death rate is found than in the southern section. Limburg found that there is no peculiarity of distribution in multiple sclerosis among sex, race, occupation, or population density The median duration for fatal cases is about 27 years There are, therefore, about 50,000 persons in the United States suffering with the disease at any one time.

Etiology—The etiology of multiple sclerosis remains unsolved, but there are certain indications which lead one to suspect an infectious etiology However, Reese (15) summarizes as follows: "The clinician has only meager support for an infectious disease process in M. S. There are nowhere epidemics of M. S. recorded. There is no febrile temperature, no perspiration, no leucocytosis, no increased sedimentation rate in the average case." Reese also states that modern medicine is not considering one causative etiologic agent in a disease alone but relates intrinsic or extrinsic factors to the total reactive defense mobilization of a host

Mechanisms.—The papers of Reese (15), Baker (16), Alvord & Stevenson (17), Kabat *et al* (18), Swank & Bessey (19), Brickner & Simons (20), Alexander *et al* (21), Tucker *et al* (22), Grain & Jahsman (23), Sperry & Waelsch (24), Finley (25), Grinker *et al* (26), Keschner (27), and Tillman (28) are essentially all concerned with the mechanisms, since the etiology is unknown. There is an analogy to this procedure in the extensive experiments now going on with adrenocorticotrophic hormone (ACTH) and cortisone. The beneficial effect of these drugs in nearly every condition where benefit is obtained appears to be on the mechanism and not on the etiology. We are, unfortunately, situated in very much the same way with multiple sclerosis.

Brickner & Simons (20) conclude their study on emotional stress in cases of multiple sclerosis as follows

1 A study has been made of the records of 50 cases of multiple sclerosis in a search for distinct clinical evidence as to whether emotional factors may precipitate attacks of the disease 2. Clinical evidence, although not scientifically final, does suggest an affirmative answer Difficulties are inherent in the evaluation of the evidence in many cases, and certainty is difficult to achieve 3 Sometimes the time interval between the occurrence of the emotional event and the development of the pathological neurological process is very short, these instances support the assumption that physiological factors linked with the emotional episodes may set off the pathological mechanism. In other cases the time interval is so long that other (physical and chemical) processes, such as anorexia or gastrointestinal disturbances, are likely to occur; these, rather than the emotional process itself, must be thought of as contributing to lesion formation 4 The evidences are sufficiently indicative of a direct or indirect relationship between stress and the precipitation of attacks to warrant doing everything possible to help patients with multiple sclerosis to avoid stress and tension

shown that gamma globulin has the ability to precipitate colloidal solutions and that albumin protects such solutions from precipitation

A technique for the determination, quantitatively, of specific cerebrospinal protein fractions has been developed by Kabat and his associates By this method an abnormally high gamma globulin content was demonstrated in 80 per cent of 81 cases of multiple sclerosis. In 22 cases the results obtained by Kabat's method are compared with those of Lange, using his recent modification of the colloidal gold test, and with the conventional colloidal gold test. Abnormalities were demonstrated by Kabat's method in 91 per cent, by Lange's test in 71 per cent, and by the conventional colloidal gold test in 33 per cent of these 22 fluids

Storch *et al.* (36) studied in detail five tests and concluded as follows:

1. The schedule of five obligatory tests, including appearance, total and differential cell count, total protein determination, the quantitative colloidal gold reaction and quantitative complement-fixation tests in both blood and spinal fluid is helpful in differential diagnosis of multiple sclerosis. 2. The most important of these are the colloidal gold reaction and the complement-fixation tests 3 The current modifications of the gold test, or substitutes for it, are of little or no value in differential diagnosis 4 The quantitative gold reaction, as performed in the Division of Laboratories and Research of the New York State Department of Health, is of considerable value in the diagnosis of multiple sclerosis 5. The syndrome, highly suggestive *but not specific for* multiple sclerosis is a clear fluid with normal or slightly elevated mononuclear count, a normal or moderately elevated total protein concentration (usually less than 75 mgm per cent), a type D (or CD) gold curve and negative complement fixation reactions both in blood and spinal fluid. 6 It is probable that deviations from this formula reflect the predominant pathologic process at the time of puncture. 7 Determination of the ratio of gamma globulin to albumin in the cerebrospinal fluid would also appear to be quite helpful in differential diagnosis of multiple sclerosis However, it is felt that the quantitative gold reaction can be performed with greater speed and accuracy, especially now that the difficulties encountered in the original technic have been eliminated Neither test is specific.

Carter *et al* (37) studied in detail the course of multiple sclerosis as determined by necropsy-proven cases and arrived at the following summary.

1. The clinical findings in 46 autopsied cases of multiple sclerosis are reported. There were 24 males and 22 females in this series In the total cases and in the males, the age of onset occurred in two peaks, the first in the decade between the ages of 20 and 30 and the second between 35 to 45 In females the peak was between 15 and 30 2 The most frequent initial symptoms were those of weakness, visual disturbance, tremor and ataxia, and paresthesiae Speech difficulties and urinary and rectal difficulties occurred late in the course of the disease Forty-eight per cent of the cases began with one symptom and 52 per cent with more than one symptom 3. The fol- [illegible]

changes in optic nerve (78 per cent), abnormal movements (67 per cent), and mental changes (61 per cent) 4 Unusual features in this series were the high incidence of muscular atrophy (48 per cent), pain (42 per cent), including 9 per cent with facial pain, and superficial sensory levels (33 per cent) 5 Leg weakness, diplopia, visual

perivascular or primarily degenerative is answered by Zimmerman & Netsky (30) in a manner contrary to the more recent reports. They say:

> More frequently than otherwise, the plaques of multiple sclerosis were not related to blood vessel distribution. No evidence was found to indicate that vascular occlusion or thrombosis was the underlying factor in plaque formation
>
> The relationship of the disseminated encephalomyelitides to multiple sclerosis was discussed and the conclusion reached that these conditions are *not the same disease entity*.

Symptoms and signs.—Rucker (31) again presented a good paper on the sheathing of the retinal veins in multiple sclerosis. The sheathing which he discussed is away from the optic disks and without visible cause, and when so found, it is usually indicative of multiple sclerosis. He concludes, however, that it does not shed light on the disease.

Savitsky & Rangell (32), in a paper on the ocular findings of multiple sclerosis, conclude as follows:

> 1. Two hundred and sixty-four verified cases of multiple sclerosis are analyzed from the point of view of ocular findings 2 The importance of ruling out concomitant disease is emphasized Eight of 50 cases had other coincidental organic disease of the nervous system 3. The frequency of supranuclear ocular palsies and their probable relation to the posterior longitudinal bundle is noted 4 Homonymous hemianopsia and isolated fourth nerve paralyses are rare in multiple sclerosis. 5. True Argyll Robertson pupils are seen in multiple sclerosis 6 Complete blindness, though rare, is occasionally encountered

Bender & Weinstein (33) made a special study of the median longitudinal fasciculus because of its frequent involvement in multiple sclerosis. Under experimental conditions, they found this structure not to be concerned with head and body movements, conjugate deviation of the eyes, or with lid closure

Jasper *et al.* (34) studied the electroencephalogram in multiple sclerosis He found that 90 per cent of the patients showed distinct abnormalities during the acute stage The abnormalities were chiefly in the form of slow waves During the subacute or chronic stage, the electroencephalogram gave no particular help in diagnosis.

Laboratory findings.—Freedman & Merritt (35) reviewed the cerebrospinal fluid findings in 2,618 cases from the literature and 250 from the New York Neurological Institute and Montefiore Hospital, but they limited their studies to changes in cell count and protein and positive colloidal reactions Their conclusions are as follows

> While the presence of an elevated cell count seems to be characteristic of the time of an exacerbation of mutliple sclerosis, there is no clear evidence that any of the other noted abnormalities are related to the clinical course of the disease Some degree of correlation has been reported between the severity of the clinical picture and the presence of abnormal cerebrospinal fluid findings.
>
> Electrophoretic studies of the cerebrospinal fluid protein have demonstrated that the gamma globulin fraction is elevated in multiple sclerosis It has been further

trauma itself cannot cause it, but may apparently awaken a disease process already potentially existent.

As for the Symptom Composite indicative of Multiple Sclerosis, it was the opinion of the Commission that the several neuron systems of the neuraxis may be involved separately, or in numerous combinations in such a way as to produce a great variety and often a kaleidoscopic display of symptoms. Any combination of symptoms indicative of a multiplicity of central lesions, not attributable to some infection or injury, warrants the diagnosis of Multiple Sclerosis.

Triad of Charcot Charcot's triad of symptoms, noted by early observers, namely, nystagmus, intention tremor and scanning speech, should not be held as a symptomatic combination necessary to the diagnosis of Multiple Sclerosis Earlier concepts of the disease were based on fully developed chronic cases in which the triad was almost invariably present This triad does not appear in many cases in the initial stages of the disease and is often absent during its entire course!

Frequency and Incidence. Multiple Sclerosis is by no means so infrequent in this country as has been held by many authorities There seem to be good reasons for believing that it is among the most common of organic diseases of the nervous system

Onset and Course Many of the symptoms in the early stages of Multiple Sclerosis are so slight and so transitory as to make little impression on the patient's recollection. These symptoms, often subsiding without trace, may occur later and progressively evolve into a fully developed clinical picture of the disease Remissions of this kind at the onset are believed to be common and probably occur in the majority of cases In certain instances, the onset, instead of occurring insidiously, may occur as an acute fulmination with the development of symptoms at the maximum intensity.

The Commission wishes to call especial attention to the early fleeting disturbances, such as impairment of vision, ocular paralyses and weakness of one or more of the extremities

Remissions frequently occur so that the suspicion of hysteria arises

Motor Symptoms Multiple Sclerosis usually manifests itself as weakness or stiffness in one or both lower extremities, gradually culminating in a spastic paralysis The motor disorder may manifest itself in the form of bulbar, cerebellar or hemiplegic disturbances The type of motor defect in the vast majority of cases results from upper motor neuron involvement In some cases, however, paralysis of the lower motor neuron variety has been observed due to the extension of the plaque into the ventral gray columns of the cord The deep reflexes are uniformly increased (90% of cases) Loss of abdominal reflexes (83 7%) is also of great frequency.

General Somatic Sensory Symptoms These occur in slightly more than one-half of the cases They are usually patchy in distribution, but objectively of the type referable to posterior column disturbance, or they may produce defects in algesic and thermic sensibility, with varying types of dysesthesia

Cranial Nerve Disorders Nystagmus, with or without ocular palsies and diplopia, constitutes the most frequent motor disturbance in the sphere of cranial nerve innervation, while temporal pallor of the disc with scotomata has a very high representation in cranial nerve disturbance According to Friesner, the nystagmus depends upon some lesion in the mechanism associating the vestibular with the oculo-motor apparatus The importance of nystagmus as a symptom in the diagnosis of Multiple Sclerosis stands unassailed Temporal pallor is one of the most valuable diagnostic signs, since it is found in practically no other nervous disease The rarity of blindness, and also the relative infrequency of swelling of the discs are diagnostic features of value in the differential diagnosis (Holden). Concentric contraction of the visual fields is looked upon with scepticism while much diagnostic emphasis is placed upon the

acuity impairment, and paresthesiae were the symptoms that remitted most frequently. Initial manifestations were more likely to remit than those which occurred late in the course of the disease. A single initial symptom was more likely to remit than was an initial complex of symptoms. 6. While other series gave a high percentage of clinical types, in our series this was true in the late stage of the disease in only 15 per cent. Division into clinical types early in the course of the disease is of some prognostic value Cases that can be early classified as mixed type had a short course, whereas the course was prolonged in those cases who were classified as a spinal type 7. The average duration of life was 13 years. The shortest duration of life was 8 weeks while the longest was 64 years Forty per cent of our cases died within the first ten years and 66 per cent died within fifteen years. The duration of the disease was only slightly affected by the age of the patient at the time of the onset of symptoms The later the onset of the disease, however, the less was the loss of normal expected years of life. Mental deterioration and sensory loss indicating a transverse lesion of the spinal cord indicated a poor prognosis An onset with diplopia or weakness was often associated with a prolonged course 8 In 37 per cent of the cases, a diagnosis other than multiple sclerosis was entertained by one or more examiners. These included neurosyphilis, spinal cord tumor, and diffuse sclerosis. Two cases were subjected to laminectomy. 9. Infections were the cause of death in 70 per cent of the cases, the respiratory tract being involved most often. Urinary infections were uncommon as a cause of death Two cases had a tumor of the brain.

Treatment.—The treatment of multiple sclerosis has been and is unsatisfactory. There is no attack as yet on the etiologic agent, which is unknown. The various methods dealing with the mechanisms, such as those suggested by Putnam (38), Langworthy (39), Lazarte (40), and Braceland & Giffin (41), are based on vasodilatation and anticoagulation. No one claims a cure; arrest or remission is the best anyone can expect at present. The re-education of muscular systems remaining to the patient offers some help

Conclusions arrived at by the Commission of the Research Association in Nervous and Mental Disease, 1921.—

For the next chapter in the development of our knowledge of Multiple Sclerosis we have herewith the conclusions arrived at by the Commission of the Research Association following the meeting of the Association for Research in Nervous and Mental Disease in 1921 and with the additional facts and theories bearing on the Symptom Complex of Multiple Sclerosis [Timme (42)]

1 The age of persons suffering from Multiple Sclerosis ranges chiefly from twenty to forty, but may occur as early as the tenth or as late as the sixtieth year. 2. Males are more frequently attacked than females in the ratio of 3 2 Multiple Sclerosis makes up about 1 to 2% of the organic diseases of the nervous system, including those due to syphilis. 3 The duration of the disease varies from less than a year to more than thirty years 4 It occurs in persons skilled in manual work more often than in ordinary laborers or in brain workers 5 In the United States it seems to occur more in the region of the Great Lakes, while in Europe it prevails more in the Northern parts than in Italy or about the Mediterranean Sea. 6 It is not a familial disease and is not inherited—with rare exceptions—but in the ancestry there is often evidence of a neuropathic stock 7 Acute infections may immediately precede the disease in about 10 to 12%—*and it occurs no more frequently in persons who have had the usual* children's diseases than in those who have not had them 8 It is not caused by syphilis 9. In a small percentage of cases it appears to be excited [illegible] but

The work of Teague in searching for a microorganism, especially a spirochete, has yielded a negative result, in spite of the findings of European observers in this regard. The Commission thought that a negative result, while not so valuable as a positive one, nevertheless in view of the histological character of the pathological process must induce a continuous appreciation of the finding of microorganisms in this disease

This concludes the findings of the Commission from the 1921 meeting of the Association for Research in Nervous and Mental Disease Let us hope that further light may be forthcoming at our present meeting

Syndromes of the Herniated Cervical Disks

When, a few years ago, it was discovered that cervical intervertebral disks can herniate as do disks in the lumbar region, it was thought that cervical herniation was a rarity. In the last year, more and more herniated disks have been found in the cervical region Moreover, it has been found that no single syndrome is characteristic but rather that a herniated cervical disk can simulate a great many classical syndromes.

The "syndrome" of amyotrophic lateral sclerosis has come into prominence. Here it should be pointed out that amyotrophic lateral sclerosis is not a syndrome, but a highly specific disease, a variety of progressive spinal muscular atrophy It is entirely wrong to report "three cases of amyotrophic lateral sclerosis due to focal lesions of the cord" In amyotrophic lateral sclerosis, there are no sensory symptoms or signs, as the disease itself is purely motor—a degeneration of the anterior horn cells in the cervical region of the cord plus a degeneration of the upper motor neuron due to death of the motor cells of the cortex Yet, a number of cases have been reported in which, superficially, the disease was simulated by focal cervical lesions including herniated disks

Bucy (43, 44), in two papers, has rendered a considerable service in calling attention to the danger of allowing patients with an operable cervical disk lesion to go on to incapacity with a diagnosis of a chronic degenerative disease such as amyotrophic lateral sclerosis, primary lateral sclerosis, or multiple sclerosis In his experience, the disk which protrudes in the midline is the most common, while a lateral protrusion simulating a Brown-Sequard syndrome is less common. Den Hartog Jager & Moffie (45) add to the list of Bucy the syndrome of subacute combined degeneration of the spinal cord. Elvidge & Li (46), in a similar vein, give an additional list of conditions simulated, namely, tumor of the spinal cord, angina pectoris, syringomyelia, and syringobulbia They found in one case involvement of the trigeminal nerve through involvement of the projection fibers in the cervical cord to and from the descending root of the fifth cranial nerve To this list can be added traumatic arachnoiditis, pachymeningitis cervicalis hypertrophica, and parasagittal meningioma as erroneous diagnoses made when a protruded cervical disk was the actual lesion Raney *et al* (47) have described headache caused by a herniated disk and relief of it by traction.

Alpers & Farmer (48) call attention to the long established syndrome of damage to the cervical spinal cord and simulation of amyotrophic lateral sclerosis through the use of the pneumatic drill They favor vasomotor influences as the mechanism; yet, it is quite probable that the tension of the

lacunar losses of visual acuity, especially in central and circumcentral scotomata.

The facial, hypoglossal and glossopharyngeal nerves appear to be less frequently involved than the optic and ocular nerves, but must be regarded as among the cranial nerves showing definite proclivity to impairment by the pathological process The defects in the cranial nerves are most commonly nuclear, but may be in internuclear, or supernuclear connections.

Mental Symptoms. The Commission concluded that there is no particular psychic disorder characteristic of Multiple Sclerosis. The formation of patches in the brain does not lead to the development of any of the well recognized forms of psychosis The euphoria may be associated with the disease but is not as characteristic a feature here as for example in general paresis The absence of mental deterioration, even where well defined pathological changes are recognizable in the cerebral hemisphere, seems to emphasize the ability of the central nervous system to adjust itself, or even withstand, serious disorganizing influences

Sympathetic System and the Endocrines. The Commission finds that there is no evidence of involvement of the sympathetic nervous system or of the glands of internal secretion This immunity seems to be due to the automaticity which the segmental mechanism of the spinal cord is capable of assuming in relation to the visceral functions when cut off from the higher influences Disturbances, however, in the control of bladder and rectum frequently occur although little is known of the exact mechanism producing these disturbances.

Serology and Bacteriology Based on the studies of the cerebrospinal fluid and blood in Multiple Sclerosis, there is nothing to indicate that a deviation from the normal [illegible]

[illegible] cluded that the spinal fluid, while it may not be normal, contains nothing pathognomonic of Multiple Sclerosis

In considering the results of the investigations in the effort to insulate the active etiological factor producing Multiple Sclerosis, the Commission concludes that at present (1921) there is no incontrovertible evidence that the causative factor has been isolated. Further development of this problem is to be carried on during ensuing years

Conclusions Concerning the Pathology of Multiple Sclerosis The papers presented and the respective discussions brought into prominence three questions. *First:* is the pathological process in Multiple Sclerosis of an inflammatory or of a degenerative nature? *Secondly:* is Multiple Sclerosis in the latest stages a sequel of an acute inflammatory process? *Lastly:* is the disease due to a microorganism?

The conclusion reached by Hassin from his careful study of a number of cases of well-developed Multiple Sclerosis was that the process is conclusively degenerative, and due to some unknown toxin—probably endotoxin Spiller, on the contrary, took exception to this view that the process is primarily degenerative and showed speci- [illegible]

[illegible] or lues? Are there therefore two types of Multiple Sclerosis [illegible] as an acute inflammatory process and later showing a degenerative character from outset? Only further research and investigation will be able to come upon a satisfactory conclusion

six cases for report in which there were signs of birth injury although the children were born at term and without artificial aid. All of this harmonizes with the now generally accepted concept that damage to the brain is a very common result of birth, even normal birth. The findings were: (*a*) microcephaly with polygyria and subdural hematoma, (*b*) traumatic hemorrhage in the right ventricle, (*c*) underdevelopment of the brain with polygyria and severe destruction of the cortex, (*d*) traumatic malacia in the parietal lobe on both sides, (*e*) microcephaly with microgyria, and (*f*) hemorrhage over right and left hemisphere and at the base of the brain. The pathogenesis of these changes is discussed. The microgyria is held to be the result of injury and not congenital. The alterations in the cortex are often seen to be spread much farther over the hemispheres than the area of the local injury. Compression of the head by uterine contractions may cause a shift of the intracranial contents and rupture of the small veins. Disturbances in circulation may follow traumatic alterations in the innervation of the walls of the blood vessels

Scholz (52) takes up the pathogenetic interpretation of complex histopathological pictures found in cerebral affections which, he says, necessitates a more precise knowledge of the elementary lesions produced by the chief physio-pathological processes generally responsible, i e, anoxemia, edema, and plasma infiltration An attempt is made to define the pathogenetic significance of tissue changes produced by anoxemia and by edema due to purely circulatory disturbances of the hemato-encephalic barrier. In this paper, he deals with the histological side of the problem; it will be followed by another in which the topographical aspects in connection with the vulnerability of different tissues will be discussed.

Slight anoxemia of nerve tissue causes disseminated necrosis of the cells leading to the typical lesion of 'blanching' (Spielmeyer), while the nerve fibers show a much higher resistance. The later stages of this necrosis are described, and it is shown that the degeneration of interstitial tissue is also due chiefly to the anoxemia The edema associated with these circulatory disturbances produces only secondary changes In edema independent of anoxemic phenomena, on the other hand, the nerve cells are found to be highly resistant, while the fibers soon show changes both in the gray and white matter Independently of this, the macroglia increases in the gray matter, whereas the microglia does not react until later Even where there are exudates rich in albumin, the nerve cells change only slowly. As the albumin content increases, however, tissue exchanges are impeded and the life of the cell becomes difficult; cellular lesions are then produced by secondary anoxemia. The various pictures produced by exudates according to their albumin contents are described, and attention is drawn to their resemblance to certain well-known histopathological pictures The significance of these phenomena is discussed in connection with serous inflammations, glial reactions in certain forms of encephalitis, and the production of gliomesenchymal reactions in Wernicke's polioencephalitis, in Wilson's disease, and in certain intoxications. These considerations are also of importance for

cervical muscles, especially the oft-repeated severe tensions and vibration in such cases may cause a herniation of cervical disks. Many of the erroneous diagnoses referred to above are made in the chronic rather than in the acute stages of the damaged disks.

Because of these developments, any case which appears with symptoms and signs of spasticity of the lower limbs, with or without signs of involvement of the upper limbs and with or without sensory symptoms, must be studied thoroughly for a cervical disk lesion. This study includes roentgenography, plain and with ethyl iodophenylundecylate (Pantopaque), fluoroscopic visualization of the ethyl iodophenylundecylate as it moves through the cervical canal, and spinal fluid examination and dynamics in detail. It has even been shown that electromyography may give information when cervical motor roots are involved.

The occurrence of nystagmus from high cervical disk lesions has been observed, though apparently not reported. It is one sign which leads the untrained to the certainty that a lesion above the foramen magnum must be present and hence that multiple sclerosis is present.

A point demonstrated by Kaplan & Kennedy (74) several years ago is of importance in the study of spinal fluid dynamics in cases of midline protrusions of disks. While the flow of spinal fluid is normal with the neck extended, it may be entirely blocked when the neck is sharply flexed. Finally, all tests may fail to show a disk because of its variable position, and yet, a protrusion may be shown at operation

Treatment of Acute Cerebral Thrombosis and Embolism

Until the year 1949, acute cerebral thrombosis and embolism were much ignored because treatment was ineffective. De Takats (49) then reported that acute cerebral thrombosis, if treated within a few hours by block of the ipsilateral stellate ganglion with procaine, would often be relieved. The stellate ganglion, located at the first dorsal vertebra, sends vasomotor fibers to the cerebral blood vessels and can be blocked through a spinal needle introduced into its immediate vicinity by 10 cc. of 2 per cent procaine solution. If the block is successful, the ipsilateral upper eyelid droops within one-half hour, usually in 10 minutes

Amyes & Perry (50) took up the work and treated a large number of patients with moderately good results They point out that the term thrombosis is not quite correct because when a thrombus has actually formed, little can be accomplished. The injection must be made within six hours to be really effective. The surprising finding was discovered accidentally that even when the wrong side was blocked, benefit was obtained, as though sympathetic fibers were partly crossed

Asphyxia and the Brain

Brouwer (51) takes up the subject of cerebral asphyxia, particularly at birth. After pointing out that asphyxia tends to occur following birth trauma in which artificial aid is given and after premature birth, Brouwer selects

their presence by suppression of cortical activity just as well as, if not better than, by signs of irritation A subdural hematoma, by its pressure on the cortex, prevents the EEG formation, and a subcortical lesion does the same from within Even in such lesions, however, the EEG is by no means infallible, as occasionally a cerebral hemisphere completely devoid of its blood supply may give a normal EEG Indeed, an anencephalic monster has given an EEG which gave no indication of absence of the brain.

Much has been developing in the field of clinical recognition of epileptic equivalents. Winans (61) reports a case of paroxysmal cough and pain about the precordium which was undiagnosed for a long time. An EEG was then reported as showing generalyzed dysrhythmia with paroxysmal 6 to 7 per second activity suggestive of psychomotor type of epilepsy. On phenobarbital alone the patient made a complete recovery. In another case, the patient complained of pain in the right upper quadrant spreading into the right chest and lower abdomen. The pains were sometimes associated with nausea and vomiting. The EEG again showed psychomotor epilepsy and on treatment with sedatives the patient went without further attacks In the third case, the patient complained of substernal pain, rapid heart action, flushing, and sweating coming in episodes of 15 minutes' duration. The patient was extremely depressed for two days after each attack. The EEG showed psychomotor epilepsy and control was obtained with phenobarbital medication.

Delay *et al* (62) also report finding epilepsy as the underlying condition in "pseudo-schizophrenia," "atypical nervous attacks," obsessions, compulsions, apparent disturbances of character, somnambulism, and headache. Cornil *et al* (63, 64) in two papers bring forth evidence to show that *petit mal* and *grand mal* are essentially the same disease By stimulation with intermittent light, they have brought out the symptoms of *grand mal* in cases of *petit mal* and vice versa, when previously only one form was present. By further applying this diagnostic method to the treatment by adding trimethadione to phenobarbital, they have obtained better control of the seizures

Cerebral Angiography

Within the last year, the science of cerebral angiography has made enormous advances While at first its use was directed toward the most obviously fertile field, that of detecting aneurysms and other vascular malformations, its use has now spread to diagnosis of tumors and other space-occupying lesions

Gradually, from the open operation technique of exposing the carotid artery or the vertebral artery, the percutaneous method has gained ground [Lima (65)] While considerable experience is required to strike the vertebral artery through the skin, the carotid is found with relative ease The radio-opaque substance used is iodopyracet concentrated solution (Diodrast concentrated solution) or Thorotrast The earlier fears that the radioactive substance, which of necessity is left in the body and settles in the liver, might

the interpretation of certain types of old, cicatricial cerebral lesions. Amyes *et al.* (53) find that in acute anoxic states, especially in illuminating gas or carbon dioxide asphyxia, infusion of 500 mg. of procaine in 500 cc. of normal saline daily for three days is of marked benefit in restoring the patient to normal.

Trauma and Parkinsonism

Paillas *et al.* (54) report on four cases of parkinsonism following head injury and state that the parkinsonian syndromes following injury to the head are due either to direct lesions of the basal ganglia by penetrating wounds or to lesions caused by the cerebral concussion. They believe that those following limb injuries are induced by lasting painful reflexes which finally create mesodiencephalic lesions. They also speak of the possibility of posttraumatic aggravation and disclosure of a mild or unrecognized pre-existing parkinsonian syndrome due to trauma. Clinically, there is progressive development of a unilateral or even segmental hypertonic state, often followed by tremor. Ocular and vegetative symptoms are scarcely found, but pyramidal signs and sensory disturbances are frequent. The evolution is progressive or slowly regressive.

Schachter (55) discusses the same problem and in general accepts the same interpretation He cites the case of a 39 year old man who was permanently incapacitated by parkinsonism after a serious fall. A stutter developed as well. It is the general opinion among neurologists that parkinsonism is not caused by trauma alone but may be precipitated by trauma. The injury should, therefore, be charged only with the precipitation and not the complete causation.

Electroencephalography

During the last year, the electroencephalogram (EEG) has advanced in certain definite directions Through extensive researches of Gibbs (56, 57), the area of the external surface of the head which represents the inferior portion of the temporal lobes has been determined. It is located about and anterior to the ear and about the eye down as far as the zygoma. This and the added fact that only the random spike represents a focal lesion have led to the determination that in psychomotor or psychic epilepsy, the lesion is in the temporal lobe in a large number of cases. Even more important is the surgical attack on this problem led by Penfield (58, 59) and followed by Bailey & Gibbs (60). In a considerable number of cases, it has been shown that removal of the anterior three (or occasionally four) centimeters of the temporal lobe in question will relieve the epilepsy. The results have not been uniformly good, but in patients disabled because of psychic epilepsy the operation is worthwhile. It is considered important to remove only the outer portion of the cortex and to spare the amygdaloid-uncus complex because its removal causes severe psychic manifestations.

Other advances in electroencephalography have been made. It has been shown that tumors, cerebral softening, or subdural hematoma may betray

mass of tortuous channels and sinuses fed by a large corkscrew of arteries and drained by greatly dilated veins. (*b*) Most glioblastomas show increased vascularity at the margins of the tumor, with sinuses, irregular dilatations, and vascular loops within the tumor. (*c*) Astrocytomas displace normal vessels by an avascular area or an area having few fine, uniform, straight or slightly curved vessels (*d*) Meningiomas show usually vascular abnormalities which give them a characteristic appearance [The snow-ball appearance is normally found in the latter part of a series of pictures] Chavany *et al.* (69) point out the advantages of angiography over ventriculography in furnishing information about tumors It is thus seen that in the study of an angiogram, one looks first for displacement of normal vessels and second for the vascular pattern of a tumor. It is now possible to make a diagnosis not only of the presence of a tumor but of its pathologic nature by the angiographic appearance.

As pointed out by the Raneys & Sanchez-Perez (67) and as seen on a number of occasions by the writer, the time has now come when too great a reliance is sometimes placed on the angiogram. When an angiogram is performed for a suspected tumor one may find an aneurysm which is entirely innocuous and quiescent. The error has been made repeatedly of attacking the aneurysm while ignoring a neoplasm which does not appear as prominently in the films as does the aneurysm In one instance, pain in the eye gave cause for an angiogram which disclosed an aneurysm. Operation for it caused hemiplegia, while the pain was shown to be due to glaucoma Failure to visualize a given artery does not necessarily mean it is thrombosed.

Elvidge & Feindel (70) have surveyed the surgical treatment of certain aneurysms of the anterior cerebral artery. The value of angiography is stressed not only in diagnosis but in planning the surgical approach. Some aneurysms can be clipped and excised, others trapped, while still others require ligation of the main artery. They point out that rupture during operation is a considerable hazard and that steps to combat the complication and its results should be taken in advance

A recent new diagnostic method has been advanced by Gass *et al.* (71) of the University of Michigan, namely, cinefluorography. This method requires considerable special equipment because motion pictures are taken of fluoroscopic views as Thorotrast circulates through the brain in 4 or 5 sec. The rapidity of the flow makes diagnosis difficult, but by speeding up the number of exposures to 60 or more per sec, slow movies can be obtained. While the method is still subject to technical improvements, it is already highly fascinating and instructive Vascular anomalies, aneurysms, and tumors can be seen as the substance rushes through the vessels.

Angiography has been improved in still another manner by Ray, Dunbar & Dotter (75), who have used diodrast in outlining the great venous sinuses of the dura mater and even veins of the brain The medium is injected by means of a ureteral catheter into the sinus, usually the superior sagittal sinus, through a trephine opening It is, however, possible to pass a vein catheter from the cubital veins of the forearm up to the jugular bulb and

give rise to trouble later have been largely dispelled as the years have elapsed without report of resulting harm.

While List has continued to work with only his marvellous skill and clinical acumen, Sanchez-Perez (67) has perfected a *seriograph*, an instrument which, by the mere closing of a switch, automatically takes a series of radiographs of 6 exposures in 4.5 sec. or 8 in 6 sec. As, in the average case, the circulation through the brain occupies 4.5 sec., the 6 exposures are usually sufficient. The patient is placed on a table with the head resting on the seriograph and the x-ray machine in readiness. With the seriograph plugged in and connected by a switch to the injecting syringe, the series is automatically started as the injection is made. The thorotrast or diodrast replaces the blood and does not mix with it; a clear picture of the vessels is thus obtained as the material flows through the cerebral vessels. The first exposure shows the beginning of an arterial picture which improves with the second and third exposures. In the fourth exposure, the veins begin to show, particularly the veins entering the superior sagittal sinus. In the fifth and sixth exposures, only the cortical veins, the Galenic veins, and the venous sinuses appear.

A first series is usually made to show the lateral views. A second injection can immediately be given to get anteroposterior views, thus providing a three-dimensional set of photographs. When the lesion is expected in the posterior fossa (cerebellum) or occipital lobes, the vertebral artery is injected. Lateral and anteroposterior views can be obtained. Of necessity, the material goes into the basilar artery, which in turn, dividing as it does into the two posterior cerebral arteries, sends one-half into each posterior cerebral artery. A radiogram of the vessels of the occipital lobes is thus obtained.

Frankel (66) has studied a series of cases in which the clinical diagnosis was migraine for as few as 12 to as many as 50 years, but in which cerebral aneurysm was demonstrated by angiography or necropsy He believes that in such cases, a change in character of the headache and/or the addition of extraocular palsies to the syndrome should alert the clinician to the development of an aneurysm or to the expansion of an already existing aneurysm.

The Raneys & Sanchez-Perez (67) report on the application of angiography to arteriovenous communications, both congenital and traumatic. They point out that if the diodrast appears in the circulation of the hemisphere ipsilateral to the injection, such a finding is evidence of insufficient circulation through the circle of Willis to render feasible a trapping operation. If the radio-opaque substance is found in good quantity on the side opposite the injection, there is good evidence of adequate communication through the circle. The authors also point out the value of angiography in giving an accurate measurement of cerebral blood flow. In arteriovenous communications, the radio-opaque substance passes out of the cerebral circulation with extreme rapidity because of the short-circuit.

Culbreth *et al.* (68) have reported on a study of 96 angiograms made for diagnosis of cerebral neoplasm The characteristics of various tumors angiographically are outlined as follows: (*a*) Arteriovenous angiomas show a

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occasionally higher. The medium then flows against the current to outline the venous sinuses. By these techniques, thrombosis of the lateral or superior sagittal sinus can be demonstrated. When a thrombus is encountered, the medium by-passes the clot by entering the cerebral veins. Under such circumstances the larger cerebral veins are visualized.

Limitations and difficulties of angiography—Technical difficulties are encountered from several different angles. First, since angiography is frequently done, careful screening of the radiations from the x-ray machine is essential to protect the workers. Lead-covered gloves are cumbersome and even prohibitive when the syringes and needles are being manipulated Brass cones have been devised to shut out all scatter of the rays and this measure may prove feasible

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In spite of the limitations, many of which disappear with increased experience, angiography has become almost a routine procedure in the study of intracranial lesions and is essential to a complete evaluation of any such case. The seriograph, at present the most perfect technical apparatus, may be replaced by rolling of films to obtain serial views as the medium passes through the circulation. Cinefluoroscopy will, in all probability, also be improved to become entirely feasible. The less well-defined contrast is offset by the actual visualization of the dynamics, since the flow of the current itself is seen

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PSYCHIATRY[1]

By Erich Lindemann

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In the last few years and especially in the year 1950, psychiatry has been in a process of adapting to the overwhelming demand of the public for services and to the need for a more solid foundation upon a basic social science which would be equally as reliable as is physiology in relation to internal medicine. There has also been great emphasis on research, particularly since financial resources for research activities became available through the Mental Health Act, administered by the National Institute of Mental Health

Another process which might be called consolidation of past gains has been going on, as exemplified by the recent publications of the Group for the Advancement of Psychiatry which are intended to clarify psychiatric concepts and make available to the profession and to the public essential information in the field of psychiatry. Since these reports are circulated among the members of the organization for amendments and criticism and, therefore, express the considered opinion of 100 or more psychiatrists, they can be regarded as presenting the views of a fair section of the profession concerning such important topics as "Psychiatrically Deviated Sex Offenders," "Basic Concepts in Child Psychiatry," and "Revised Electro-Shock Therapy Report " Some significant developments in specific fields may be summarized as follows

Brain Functions

The function of the cerebral cortex, especially of the temporal lobe.—Penfield (1) has described with great care the electrocorticogram and the response to electrical stimulation of the exposed cortex of epileptic patients who underwent surgery for the removal of tissue which was thought responsible for the seizures Of special interest are the disturbances in speech which follow stimulation of the frontal, temporal, and parietal areas in the dominant hemisphere adjacent to the speech areas. His observations also lead to better understanding of the functions of the temporal lobe After the temporal cortex has been under the influence of epileptic discharges, "psychic" mechanisms may be activated by electrical stimulation here Also, hallucinations similar to those experienced spontaneously during so-called psychomotor attacks may be produced, even fairly elaborate sequences of imagery similar to dream states It is also possible to produce perceptual illusions by stimulating this area. There may be found phenomena such as the fading of voices,

[1] This review covers the period from the beginning of the year 1949 to October, 1950.

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medical practice has opened a new field for psychiatry because of the attendant mental changes observed after the administration of the substances The findings concerning possible beneficial effects in mental disease allow no conclusions at present Of very great significance is the observation that individuals who have a severe somatic symptom (for instance, rheumatoid arthritis) and are relieved from the somatic distress may develop a psychotic episode in the course of their improvement. Whether this type of episode is directly related to changes in central nervous system functions or has to do with the emotional disequilibrium produced by the sudden removal of symptoms and the loss of psychological defenses against overwhelming emotional reactions is a question under considerable debate [Ludwig (5)].

Psychosomatic Disorders

"Life Stress and Bodily Disease," the proceedings of the December, 1949 meeting of the American Association for Research in Nervous and Mental Diseases (6), presents an impressive array of reports concerning a great variety of abnormalities of visceral functions observed in time relationship to different forms of emotional strain There is conspicuous progression from the older notions that a special kind of personality might be found regularly associated with a special kind of somatic disease to the concept that unspecific weaknesses in the personality structure and a variety of kinds of stress may, in combination, be responsible for morbid alterations of visceral functions The anecdotal account of individual life histories has been supplemented by detailed study of visceral functions in experimental situations. The more or less regular co-occurrence of certain personality traits and behavior patterns with certain types of illness is subjected to statistical treatment [Saslow (7)]. The great significance of separation from emotionally supportive persons through death as a source of severe emotional strain was demonstrated, especially for ulcerative colitis [Lindemann (8)] Wolff (9), who was responsible for the organization of the material, concluded that the best formulation as of today would seem to be that certain visceral organs at times of emotional stress participate in primitive defensive or offensive reactions of the organism by the mobilization of fight or flight patterns when mastery of a situation by integrated behavior becomes impossible. There are, in all probability, many variations in the chain of links between somatic disorder and emotional strain.

Cobb, in his book *Emotions and Clinical Medicine* (3), divides the type of symptom formation which may ensue from emotional stress into six categories· (*a*) symbolic dysfunction, i.e., the development of conversion symptoms, (*b*) the use of certain easily available physiological reflex mechanisms such as "hysterical vomiting," (*c*) the development of primitive protective reaction patterns as formulated by Wolff and as illustrated by the hyperactive colon being involved in "ejection and riddance" as a reaction to a hostile environment, (*d*) visceral changes with anxiety or excitement which, as conditional reflex, may become related to some trivial signal in the environment

momentary alteration of [illegible]

responses.—The increasing interest in the temporal lobe and the adjacent structures of the archicortex has been documented by MacLean (2) in a review of "Psychosomatic Disease and the 'Visceral Brain'." His formulations are based on the Papez theory of emotion, which asserts "that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their connections constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression." The rhinencephalon, to which MacLean refers as "the visceral brain," together with "the orbitomesial surface of the frontal lobes, the anterior insula, the temporal pole, and the pyriformamygdaloid complex are mutually related in their bearing on autonomic activity and emotional behavior"

Cobb (3) has elaborated this concept of the anatomical background of emotional responses by a review of the present knowledge concerning the comparative neurology in the mammalian series of the neocortex and the archipallium, and by a review of the experimental facts concerning the differential responses of different animal species to decortication experiments, which may produce either sham rage in cats (carnivora) or placidity in monkeys. The great complexity of the anatomical and physiological processes underlying emotional responses is paralleled by the difficulties in the psychological field of identifying in a clearcut manner a specific emotion or classifying emotions, giving proper regard to the subjective aspect, the expressive aspect, and the "feedback" aspect of the effects of the emotions on the environment.

Selective partial ablation of the frontal cortex.—A large team of workers has systematically studied the effects of excision of various areas of one or the other frontal lobes in the so-called "Greystone Experiment" (4). This experiment is a detailed and controlled study of topectomy in mental disorders. The large body of observations assessed concerned preoperative and postoperative physical, neurological, psychiatric, psychological, and biochemical responses of a series of psychotic patients as compared with a matched series of patients not undergoing surgery There were a large number of negative findings. A battery of 67 psychological tests showed no intellectual damage contributable to the operation. The characteristic and persistent change had to do with anxiety and affective responses The most significant areas so far as alteration of the psychoses went were Brodman 9, 10, and 46. The best clinical success was obtained in patients who showed a lively affective response before the operation Once affective deterioration has occurred, there is little response to the operation The incidence of convulsive seizures was 16 per cent.

Hormonal Factors

The introduction of adrenocorticotrophic hormone and of cortisone into

Human Relations, published jointly by the Tavistock Clinic in London and the Center for Group Dynamics in Ann Arbor, Michigan, *The Sociological Review*, and *The American Anthropologist*.

Developments in social psychiatry have come to include fundamental considerations of socialization processes in which children are inculcated with the norms and expectations of the culture in which they have to live Eriksen (16) has brought together case studies in various cultures and descriptions of children's adjustments in our culture with due emphasis on uniformities and differences. The so-called cross-cultural survey [Murdock (17)] has brought together for reference purposes a very large body of information about several hundred different cultures which should serve as a basis for comparative studies of the effect of child rearing methods on adult beliefs, attitudes, and practices. The features in our western culture which present sources of strain for all individuals sharing the culture or for special groups such as the American housewife have come to attention The question, what kind of personality is likely to be found regularly connected with certain basic emotional attitudes and practices, has been raised, and we may soon have a partial answer based on this type of study.

Dicks (18) reports a thorough study made during the last war concerning the personality traits of those individuals who were enthusiastic supporters of National Socialist ideology in contrast to those who were not. He has demonstrated that psychoanalytic concepts can well be used for the analysis of interview data and then be treated in a statistical manner. The essential features of the structure of any social system as a distribution of roles and statuses in a hierarchy with the possibility of role confusion and disparity between status aspiration and status realization and the development of a systematic sociological theory of human behavior which can be articulated with psychoanalytic theory has been described by Parsons (19). There is also a renewed emphasis on epidemiological approaches to the phenomena of mental disease and abnormal behavior. Mayer-Gross's study (20) of a rural area in Scotland in terms of incidence and prevalence of behavior disorders and a symposium of the Milbank Fund (21) bringing together what is known at present about the epidemiology of psychoses and neuroses are steppingstones in this direction. Together with this development, there is a strong emphasis on community psychiatry and the integration of preventive psychiatry with the broader field of preventive medicine as carried on in schools and departments of public health [Leavell (22), Lemkau (23), and Aberle (24)]

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setting off a terrifying state of symptoms seemingly without reason, (*e*) "scapegoat" reactions in which physical impairment such as strabismus or the remnants of a birth injury may become the central concern of a patient and lead to protracted anxious preoccupation with the abnormality which seems to serve as an explanation for social and emotional inadequacies, and (*f*) physiological infantilism (as postulated by Ives Hendrik), which means a tendency to discharge reactions to a conflict into those organs where the physiological lability of normal immaturity has been retained or can be re-established Rappaport (10) has just published the second edition of his book *Emotions and Memory*, a classic in this field, which reviews the literature and cites a series of challenging experiments. They add to the slowly growing body of objective information concerning the validity and limitations of psychoanalytical concepts such as repression.

The protracted nature of psychotherapy with the severe neuroses and with the psychoses leads to ever-new search for methods to abbreviate or make more flexible the therapeutic process. There has been a keen revival of *interest in the use of hypnosis. Brenman (11) of the Riggs Foundation* has made a detailed study of behavior patterns related to different depths of hypnosis and has made systematic use of hypnosis, not so much for purposes of suggestion and for the removal of symptoms as for the facilitation of auspicious forms of transference and for the uncovering of emotionally disturbing events There also has been increasing emphasis on the significance of controlling the emotionally relevant human environment of a given patient during his course in a hospital. An appropriate distribution of roles of the various members of the therapeutic team may do much to facilitate or impair the success of a therapeutic plan [Stanton (12)].

Social Psychiatry

There has been significant emphasis on team work among psychiatrists and members of allied professions for the attainment of greater clarity in dealing with basic issues of social science. While neuroanatomy and neurophysiology were accepted as part of everyday considerations, the findings of anthropology, sociology, and social psychology have, up to now, been used only to a limited degree. In order to facilitate progress in this direction, face to face contact in joint committee work has proved useful In such a manner, many psychiatrists have become acquainted with the importance for social [illegible] as Parsons' *The Structure* [illegible] *and Culture* [illegible] hese books [illegible] present efforts to develop a logical, consistent, comprehensive, and adequate conceptual scheme which would serve as a basis for making predictions concerning the behavior of an individual in a given context of human relations. Among the journals followed with increasing interest by psychiatrists are *Human Organization*, published by the Society for Applied Anthropology,

DISEASES OF THE RESPIRATORY SYSTEM

By George W. Wright

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This review does not extend beyond October 1, 1950 but does include publications dating more than one year prior to this date. It is the reviewer's aim to note and discuss communications bearing on specific topics It is obvious that brevity prevents mention of numerous publications of merit and will not allow the coverage of other topics of equal interest and importance.

Methods

Roentgenography of the chest has been made the object of careful scrutiny regarding "consistency of reading" error by Garland (1), Sosman (2), and Fletcher & Oldham (3). It is rather surprising that studies of reading consistency are only now being made. The great importance of the human element in roentgenogram interpretation is strikingly displayed by the finding of these authors that readings of identical films by different well trained and experienced individuals show a variation of 9 to 24 per cent in regard to what was considered a positive (abnormal) film Rereading by the same individual showed a variation of 3 to 31 per cent. After establishing a clear semantic basis between the readers, the intraindividual variations diminished, but there was no effect on the interindividual variations. These studies in no way condemn the radiographic procedure, rather, they further refine the technique of roentgenogram reading and alert us to a hitherto inadequately appreciated source of error Knowledge of the possibility for disagreement by readers should make it imperative that repeated readings by the same and other observers be practiced in all borderline cases, especially in those where clinical evidences run counter to the interpretation of the roentgenogram

Until recently, bronchography has been confined to a mapping of the bronchial system, with no attempt to study the physiologic variations it exhibits By means of "serial bronchography," di Rienzo (4, 5) has explored the changes in caliber and length exhibited by the bronchial system during such acts as breathing and coughing He has also studied the variations brought about by some of the pulmonary diseases The shift of emphasis from a static to a dynamic bronchial system should do much to advance our understanding of the basic pathophysiology of the diseased respiratory apparatus The meticulous attention to detail and the considerable equipment and manpower required to accomplish an adequate technique will not easily recommend this procedure as routine in all clinics Its use as a research tool has been strikingly demonstrated by Di Rienzo, but its practical possi-

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attention to dynamics of breathing, are procedures adapted to office use and will provide information that should detect the great majority of those persons suffering from respiratory impairment.

Quite properly, much stress is currently placed upon the dangers of arterial hypoxia. Although, in the reviewer's considered opinion, hypoxia per se rarely is the primary cause of disability in man, whenever arterial hypoxia occurs as a complication of surgery or severe cardiac or respiratory insufficiency, the lack of proper supply of oxygen to the tissues may be of vital importance. Because cyanosis fails to develop until hypoxia is severe, a more sensitive method for detecting the condition is desirable. Arterial puncture and analysis of the blood is too time-consuming to be clinically practicable. Wood & Geraci (13) have developed an oximeter using two photo cells with color filters such that the output of one cell is a function of the amount of ear tissue and oxygenated blood plus reduced hemoglobin, whereas the output of the other cell is a function of the ear tissue with the amount and degree of oxygenation of the hemoglobin A comparison of the outputs can be read directly as percentage of arterial hemoglobin combined with oxygen. The careful manner in which this instrument was checked against directly measured hemoglobin saturation assures one that it will indicate the degree of arterial hypoxia with a sensitivity and range entirely adequate for clinical purposes

It is noteworthy that several papers concerning the anamnesis have appeared recently. Abrahams (14) has commented on several points of considerable importance The "insatiable appetite for laboratory investigations and other adventitious aids to diagnosis" mentioned by Abrahams as being exhibited by the medical student is commonplace and shared by many trained during the past 20 years While not in any degree deprecating the value of laboratory procedures, Abrahams, in the following quotation, makes a point that is all too often overlooked: "It is no great matter to be able to identify a cardiac lesion, the much more difficult art, as embodied in the amnesis, is to consider how many of the symptoms presented are the result not of structural lesions but of fear, anxiety, or uncertainty " The employment history is neglected to an even far greater degree in usual clinical practice. Meiklejohn (15) makes a point that should be universally appreciated but definitely is not, namely, that "It is not sufficient to name the workman's occupation." The employee categorized as a miner may follow one of several tasks, not all of which expose him to a pulmonary hazard The importance of obtaining a detailed industrial history should be evident

Pulmonary Disease of Industrial Origin

The chest roentgenogram is usually the earliest and single most striking feature of each of the specific lung diseases caused by exposure to an industrial environment Mass radiographic survey programs and plant radiographic surveys are disclosing large numbers of roentgenograms which show nodular densities of varying characteristics. The burden of proper diagnosis

bilities as a clinical procedure remain to be demonstrated. The long neglected bronchial system now has a method by which it can be studied.

The technique of angiography as applied specifically to the heart and lesser circulation is assuming a role of increasing importance in pulmonary disease. Morgan (6) points out that the procedure is accompanied by two serious risks. There is an appreciable mortality rate (approximately 1 per cent) in most clinics. It is believed that this risk is much greater in pathological subjects by reason of their debility. Repeated injections in the same individual at a single sitting also appear to increase the hazard. It is apparent that something more than idle curiosity should prompt the use of this technique. Carvalho (7) asserts that no fatalities or severe reactions have occurred when 75 per cent disodium-N-methyl-3,5-diiodo-chelidimate [Opaxil (Schering)] is used. A second hazard discussed by Morgan (6) is that caused by exposure of the radiological personnel to dangerous amounts of radiation.

The high cost of and delay in obtaining the results of radiological examinations at times acts as a deterrent to the adequate examination of the patient. Morgan (8) suggests that technical advances now available indicate the probability of greatly enhancing the quality of photofluorograms and of processing them virtually at the bedside. The realization of these two aims would be welcome indeed.

The technique for measurement of several aspects of pulmonary function have been discussed in considerable detail by authorities in their field in Volume 2 of *Methods in Medical Research* (9). Those interested in developing the facilities for estimating pulmonary function on a more objective basis than provided by the usual clinical methods will find the techniques plus comments well and completely presented in this volume. The authors do not attempt, however, to describe the application and integration of these tests in the problem of exploring the mechanism underlying the complaint of dyspnea, etc., nor do they attempt to describe how one should proceed to estimate the over-all respiratory status of a patient These two problems are well discussed by Baldwin, Cournand & Richards (10) Their paper goes far toward supplying the long needed source at which the neophyte, in studying the clinical aspects of pulmonary function, may begin. Warring (11) has written a somewhat less inclusive paper depicting the practical application of the simplest tests He properly stresses the great value of careful fluoroscopy in studying respiratory dynamics. The American Trudeau Society subcommittee on pulmonary function tests (12) has reviewed this subject, especially from the point of view of studying patients prior to collapse therapy. These communications cannot be reviewed in detail but will well repay careful reading. They stress the need for detailed questioning of the patient's past history and present complaint. The common statement, "the patient complains of dyspnea" without further comment as to the circumstances evoking this complaint is strongly deplored Measurement of the maximum breathing capacity and a careful fluoroscopy, with particular

emphysema that may occur in persons in or out of dusty trades. The authors give no data concerning the total number of men in the trade in these areas, and one cannot judge, therefore, the significance of their 10 cases.

Measurement of the influence of anthracosilicosis on pulmonary function has been reported by Motley *et al.* (22) Since it was not stated to the contrary, it must be assumed that all of the cases studied were bona fide examples of silicosis. Motley *et al.* confirm the work of several other investigators, to whit, that no correlation exists between the functional impairment and severity of changes observed in the chest roentgenogram. It is apparent from their studies that in so far as abnormal function is concerned, no significant difference exists between silicosis developing in the coal mining industry and that which occurs in other industries The chief crippling factor appears to be obstructive emphysema. These studies, as is true of all others published to date, are difficult to interpret in terms of actual disability for "work at their trade" on the part of the men examined. It cannot be safely assumed that a reduced maximum breathing capacity or mild arterial hypoxia incapacitates a person for work. Studies such as these also do not give a proper appraisal of the severity of silicosis in industry. The cases having no complaints are commonly undiscovered and rarely volunteer for study. Examination of all employees of a given plant and complete study of all silicotics thus discovered is necessary in order to evaluate this aspect of the silicosis problem properly.

An evaluation of aluminum therapy and prophylaxis for silicosis has been ably presented and discussed by Brown & Van Winkle (23). The consensus of investigators in this country is that the relief of symptoms which follows the inhalation of powdered aluminum in 30 to 50 per cent of those under treatment is predominantly a psychological effect It is also known now that at least some of the persons who had exposure to free crystalline silica with or without actual silicosis prior to their treatment by the inhalation of aluminum have developed silicosis or have shown progression of pre-existing silicosis in spite of aluminum treatment. No evidence is available as yet concerning the protection of persons without previous exposure to silica but who were exposed to hazardous quantities of silica during the period of prophylactic treatment by aluminum inhalation Although animal experiments clearly show the protective action of aluminum, it seems regrettably improbable that critical evidence in humans will be obtained.

A drama of great interest which may or may not have its counterpart in this country is currently *transpiring in south Wales As related by* Fletcher (24, 25), although it had been believed for years that virtually no disabling pneumoconiosis existed in the coal mining industry, during the past 15 years 17,000 miners have been certified as having silicosis or pneumoconiosis (solely on the basis of roentgenogram), and of these 10,000 have been certified in the years between 1945 and 1948 in the south Wales area.

in these instances becomes the responsibility of the radiologist and internist. False and premature diagnosis, caused largely by the ill-advised assumption that all nodular densities occurring in those exposed to environmental dust and fumes are of necessity due to the action of these contaminants, produces a serious degree of anxiety and confusion among the employees and employers. King (16) has made a list, admittedly incomplete, of 74 medical entities that may be characterized by nodular densities in the lung roentgenogram. Pendergrass & Robert (17) discuss in considerable detail the common diseases that must be considered in the differential diagnosis of nodular densities. Their statement, "The necessity, however, for correlating the roentgen findings with all other essential data before making a definite diagnosis is emphasized," cannot be stressed too strongly. It is the reviewer's conviction that it is very difficult to eradicate the psychological effects caused by a diagnosis later shown to be in error. This is especially true in the case of an industrial disease and indicates the need for great caution in advising the examinee that he "may have" *a chest condition of industrial origin.*

Additional cases of stannic oxide pneumoconiosis are reported by Cutter *et al.* (18) and Dundon & Hughes (19). The latter present a case complete with necropsy findings The evidence presented substantiates the designation of this pneumoconiosis as benign.

Dunner (20) has expanded his previous report of dock workers handling grain, seed, iron ore, and sulfur to 100 men. Of these admittedly selected cases, 71 have been found to have an abnormal chest roentgenogram and, of these, 36 had active tuberculosis (positive sputum). A superficial reading of this paper might lead one to conclusions not intended by Dunner. The author carefully indicates that his observations do not give a true picture of the incidence of tuberculosis in dock workers. His material is drawn from a tuberculosis dispensary and naturally will have a high incidence of tuberculosis. A survey of all dock workers must be made before the true incidence of tuberculosis and abnormal roentgenograms can be determined. The reviewer considers it unfortunate that the title of the paper fails to indicate that these workers had a mixed exposure to dust including, as noted by the author, hazardous amounts of silica. A more meaningful interpretation of Dunner's studies will be forthcoming when necropsy material is made available It is possible that he is dealing primarily with a modified silicosis

Dunner, Hardy & Bagnall (21) report what they believe to be a new form of pneumoconiosis caused by exposure to sulfur dioxide fumes and dust from coke fires. They state that 10 of 50 or 60 workers so exposed and examined by them have chest roentgenograms characterized by irregular patchy fibrosis involving both lungs, but usually predominant in one Evidence of emphysema is present in all In the reviewer's opinion, the authors' conclusions are poorly substantiated, though the findings warrant further study. The description of the roentgenograms and the appearance of those published seemed classical for the ordinary case of obstructive

suggests that, contrary to the belief of some, the acute pneumonitis can develop in the absence of the soluble salts, and that it is not the acid radical but the beryllium ion itself that is the important causative factor. The acute pneumonitis, distinguishable from the chronic pulmonary granulomatous form clinically and histologically, has not been reported thus far to progress in any case into the chronic pulmonary granulomatous form. The absence of a link between these two clinical entities suggests that their causative factors are distinctly different. The industrial exposure in the cases reported by Aub & Grier (35) is of the sort known to be associated with the chronic form. It will be important, therefore, to follow his cases to learn whether or not any of them subsequently develop the chronic granuloma without additional exposure to beryllium

The responsibilities of the medical expert testifying in regard to pulmonary injuries arising out of employment are a matter of increasing concern. The danger that a physician may misuse the prestige of his profession in this role is considerable. Compensation of an employee for injuries arising out of employment is a socioeconomic field of co-operative endeavor between employer, employee, and compensation administrator that is still new and subject to all of the shortcomings of immaturity. The obligation of the well-trained and informed physician to participate in this field is undeniable. It is as much a part of his job as is the usually more pleasant, rewarding task of administering to those ill from nonoccupational causes. Wright (36) discusses the particular responsibility of the medical and expert witness whose task it is to shed light upon the validity of the medical aspects of a claim for disability compensation. The author believes that physicians are directly responsible for a part of the difficulty which attends the administration of workmen's compensation and suggests that the situation might be improved if the expert witness gives careful consideration to that which is known to be factual as distinguished from speculation A clear understanding of the legal definition of disability and a full appreciation of the actual limits of the physician's ability to recognize and quantitate the existing degree of cardiorespiratory dysfunction would also be helpful Discrimination between occupational as opposed to nonoccupational or natural causes for the disability is essential

Tuberculosis

Edwards & Drolet (37) point out that although the tuberculosis death rate for the United States has fallen from 45.8 per 100,000 in 1940 to 33.5 per 100,000 in 1947 and is probably approximately 30 per 100,000 now, the situation for tuberculosis control is not as favorable as this data may appear to indicate. There has been a sharp upward trend of new cases registered (presumably active) with the individual state health departments, 133,837 new cases being registered in the year 1947 as compared to 100,772 in the year 1940 While some may seek refuge in the thought that the increased

The situation appears to be peculiar to south Wales, and the pneumoconiosis, though including frank silicosis, has a large component for which coal dust alone is thought to be the responsible agent The pathological lesion caused by coal dust is described by Heppleston (26) as being a focal accumulation of dust at the division of a respiratory bronchiole, associated in more advanced lesions with a small amount of fibrosis in the focal area and quite extensive perifocal emphysema The problem, incompletely worked out, is of considerable medical and economic importance.

Chronic pulmonary granulomatosis of beryllium workers has been the subject of continued study. The clinical aspects have been well described (27 to 30) as being characterized by an insidious onset of exertional dyspnea, weight loss, intractable cough, cyanosis, and a history of exposure to beryllium or one of its compounds plus, of course, the striking appearance of the abnormal roentgenogram. The pathology of this disease as described by Vorwald (31) is that of a diffuse granuloma with much fibrosis and thickening of the alveolar septa. The enormous number of blood vessels (presumably pulmonary artery capillaries) that are distant from air spaces affords ample explanation for the cyanosis and dyspnea. The somewhat cumbersome name given this disease complex is retained in preference to the term "beryllium poisoning" because as yet no one has been able to prove definitely that beryllium is the actual cause of the disease. Davies & Harding (32) believe they have produced a lesion in rats by intratracheal injection of amorphous beryllium oxide that is similar to the granuloma of humans They admit, however, that it may be a foreign body granuloma. That this disease occurs in others than actual workers industrially exposed continues to be evident, as shown in the report of "neighborhood" cases by DeNardi *et al.* (29) and Chesner (33). Because of its delayed nature and the fact that it can occur outside factory personnel or areas (exposure to broken fluorescent lights), this disease may be more widespread than it is now known to be Until recently, the treatment of the disease was very limited, amounting to supportive and symptomatic care Kennedy *et al.* (34) report marked clinical improvement during treatment of a single case of pulmonary granulomatosis with adrenocorticotrophic hormone (ACTH). This observation has been amply confirmed in the experience of the reviewer and others using either cortisone or ACTH. Improvement is maintained so long as treatment continues, but relapse occurs on discontinuance of the drug after short term therapy. No observations are available concerning the question of relapse after discontinuing therapy of several months' or more duration.

Although it has been known that an acute pneumonitis (oftentimes fatal) might develop as a result of exposure to beryllium compounds generated during the extraction of the metal, it has only recently been shown by Aub & Grier (35) that a similar acute pneumonitis can also occur from the inhalation of dust and fumes of pure beryllium oxide and also pure beryllium metal. As stated by the authors, this observation is important because it

Without much in the way of recognition, the fundamental work in this field is being carried out with a tenacity that merits more notice. Long's discussion of modern thought concerning native and acquired resistance is best quoted:

> We are left thus with a concept of resistance that includes native and acquired resistance, and recognize the fact that native resistance is in part a manifestation of rapidly developing resistance In either type prompt localization of invading bacilli at the point of entry is a significant element. The concept must also include recognition of the fact that in the highest levels of native resistance bacilli are quite unable to multiply, and inflammatory response is very slight. It is perhaps not far fetched to compare this inhibition with that occurring when tubercle bacilli are exposed in a good culture medium *in vitro* to the action of a suppressing antibiotic.

Long's discussion makes one even more acutely conscious of the fact that treatment for tuberculosis is for the most part empirical. Even chemotherapy and surgical resection, though direct, must be considered in the light of little understood or completely unknown aspects of tissue resistance to the tubercle bacillus

Mitchell & Knudson's analysis (44) of the experience of 289 cases of active minimal pulmonary tuberculosis during the ensuing seven years after treatment by modified bed rest raises a number of interesting questions. The authors found a cumulative incidence of reactivation of 37 per cent during the period following initial treatment with modified bed rest of 2 to 56 weeks' (mean of 8 weeks) duration. The late results were considered favorable in that, excluding those dead from nontuberculous causes, only 7 per cent were chronically ill or dead from tuberculosis, and the remainder were well and working after seven years The authors believe also that their study indicates that a newly acquired minimal lesion is potentially more hazardous than an older minimal lesion Strictly speaking, this study and many like it regarding tuberculosis therapy are not really assessments of the value of bed rest, etc To make conclusions in this regard requires controls of similar cases who did not receive bed rest, etc. Experience (fallacious though it may be) indicates that persons having active tuberculosis who continue in the same daily regime of work appear to do less well than those who change their routine by accepting treatment of one sort or another. Rarely, however, is the prescribed treatment confined to a single change, and for this reason, the therapy of tuberculosis, to a greater extent than almost any other disease, is extremely difficult to evaluate This is recognized in a degree by Mitchell & Knudson (44) in their conclusion #7: "There is need for controlled and comparative studies to assess the relative merits of modified bed rest, more lenient regimes, and the strict bed rest regimens used in the treatment of minimal pulmonary tuberculosis" It is also expressed by these authors when they indicate that their study does not settle the question of correct treatment for minimal tuberculosis but that it does

number of cases discovered is the result of mass surveys, Edwards & Drolet question this and infer that there is actually a larger number of discovered and undisclosed cases in the United States now than in 1940. They cite overtime work and inadequate housing of the war years, together with a large influx of Puerto Ricans and displaced Europeans who are liable to suffer a higher incidence of tuberculosis as possible factors involved in the upsurge of registered cases of tuberculosis in the United States. Their evidence clearly indicates that the problem of treating the tuberculous and protecting the nontuberculous is far from solved.

The technique of mass survey came into being primarily in an effort to discover and appropriately care for the extant cases of pulmonary tuberculosis. As is to be expected with any new technique, experience has revealed the weak points that need attention. Silverman (38), Christie (39), Cauley (40) and Boucot & Cooper (41) report on the fruits of such surveys Where good follow-up of the screening procedure is performed, 0.1 per cent or less of the total number studied in large urban areas have been found to have active (presumably requiring treatment) pulmonary tuberculosis. This may seem on superficial consideration a small yield for the tremendous effort that is put into these studies, especially since oftentimes there are no beds available for the segregation and treatment of these patients Reflection concerning the public health aspect of the discovery of these cases should convince all of the inestimable value of the surveys. Tuberculosis, being a communicable disease, is spread by contact, in the United States, almost entirely by human contact since milk and water supplies are generally very well controlled. As pointed out by Boucot & Cooper (41), those persons discovered by mass survey are generally anxious to protect others from infection and to take advantage of available treatment. It is the responsibility of the physician to see to it that those objectives are achieved and in this way to diminish the number of persons infected by those having active tuberculosis As indicated by all of the authors quoted, inertia on the part of the physicians and other workers, with a consequent delay between the taking of the film and subsequent careful check of the suspected individuals, will not impress those having active tuberculosis with the great need for treatment or the proper respect for their disease A well conducted survey is, as discussed in detail by Garland (42), a highly co-ordinated, co-operative effort Less than perfection from this point of view detracts enormously from the value of the study and makes resurvey or continuation of survey undesirable to many This procedure, which seems so valuable as a public health measure, may by ill-considered action be endangered in regard to its potentialities. If the data cited by Edwards & Drolet (37) have one important significance, it is that the seed bed of tuberculous infection in the United States is inadequately disclosed

An historical review and condensed statement of present day thought concerning resistance to tuberculosis has been presented by Long (43)

and the reduction of sputum and cough is a marked advantage in preparing the patient for surgery. The second indication is that of palliation. The reduction of sputum and cough affords considerable relief to the emphysematous, far advanced case with an intractable cough and very low expulsive power. Although an occasional cavity was observed to close and remain closed by intracavitary drainage alone, the authors believe its greatest usefulness will be found in preparing patients for other surgery.

Thoracoplasty is achieving further recognition as a definitive therapeutic procedure for pulmonary tuberculosis. In nearly every series of long term follow-up, the data show that approximately 65 per cent of those subjected to thoracoplasty are well and able to work. Kinsella *et al.* (53) have reviewed 613 long term results in tuberculous patients from a single institution. They report 66 8 per cent as being alive 5 to 26 years after the operation Another 5.55 per cent, who died of nontuberculous causes and whose tuberculosis was under control at the time of death, may be added, bringing the total to 73 35 per cent who experienced control of their tuberculosis as a result of a thoracoplasty. No attempt to break the figures down into those able or not able to work was made. While these crude figures reveal the efficacy of thoracoplasty under the most unpropitious circumstances, they do not portray accurately the effects of thoracoplasty when more selective criteria for choice of patients are used. Thoracoplasty, having been throughout the years the treatment of last resort, has been forced to earn its place by application to the most unfavorable material What the long term end results of thoracoplasty in more favorable lesions would be is not clearly determined Rubin & Klopstock (54) have attempted to explore this problem by analyzing the results of thoracoplasty in 168 patients divided into categories according to the type of disease present prior to operation. Of the entire series, the early results revealed cavity closure and sputum conversion in 76.8 per cent Two to six years later, 141 of the 168 patients were still under observation, and of these, 63 1 per cent, the familiar percentage in most studies, were clinically well. In contrast to this figure, of the 77 cases of unilateral fibrocaseous tuberculosis in the series, 80.6 per cent were clinically well at two to six years At a similar date, 60 per cent of those with giant cavity, 41 7 per cent of the fibroid, and 40 per cent of those originally having caseocavernous lesions were clinically well This study demonstrates a point that has been undoubtedly long recognized but not illustrated quite so nicely before Tuberculosis presents so many degrees of severity, types of reaction, and bacillus-host relationships that it is not always wise to consider the merits of therapy on the basis of results in large heterogeneous groups.

Thoracoplasty in the patient with severe emphysema and low respiratory reserve is a hazardous procedure because of the likelihood that paradoxical motion of the unsupported chest wall will further impair respiration and coughing. Several clinics have utilized lucite ball plombage in order to create the desired thoracic defect without the complication of a dangerous soft

provide an experience to which another study of a different form of treatment may be compared.

Wright, Place & Princi (45) have shown that fully established pneumoperitoneum is a far more effective method for reducing the size or state of distention of the lung than is paralysis of the hemidiaphragm. Pneumoperitoneum plus recumbency changes the size of the lung when measured at the end of quiet expiration (mid capacity) by an average of 46 per cent and is the equivalent in this respect to a pneumothorax of the usual therapeutic magnitude. This procedure was observed to reduce the maximum breathing capacity only slightly. From a physiological point of view, this form of therapy has many obvious advantages over paralysis of the hemidiaphragm or pneumothorax. No critical data as to the long term (post abandonment) therapeutic effects of pneumoperitoneum have been reported, but its immediate effects are very encouraging. Howlett (46) has presented an excellent, conservative view of pneumoperitoneum as a therapeutic agent in tuberculosis. Publications setting forth more recent experience with this form of treatment would be of considerable interest

Hayes (47) has reviewed the present status of pneumothorax as a therapeutic agent for the treatment of tuberculosis The modern methods of managing a pneumothorax case with early abandonment if effective collapse is not obtained and all adhesions can not be severed has reduced the complications but, at the same time, limited the utility of the procedure. Hayes points out that many cases that would previously have received pneumothorax are now recognized at once as being by preference treated with thoracoplasty. The advent of streptomycin and its use simultaneously or sequentially with pneumothorax has, to the reviewer's knowledge, stimulated a reconsideration of the indications for pneumothorax, but no definitive data regarding this point have as yet been published.

The feasibility of pulmonary decortication in chronic tuberculous empyema has been amply demonstrated by, among others, O'Rourke, O'Brien & Tuttle (48), Mulvihill & Klopstock (49), and Weinberg & Davis (50) This operation is warranted if for no other reason than to permit the obliteration of the empyema space, thereby curing the empyema. If coincident improvement of function occurs, this is an added advantage Wright *et al* (51) point out that postoperative improvement of pulmonary function does not occur in all cases of tuberculous empyema that are decorticated. A lung, the parenchyma of which has been rendered nonfunctioning by virtue of intraparenchymal tuberculosis, may distend sufficiently to obliterate the empyema space but need not return to proper function.

Woodruff, Kelley & Stranahan (52) have demonstrated that intracavitary drainage (Monaldi) of tuberculous cavities has two genuine indications for use. In the large cavity, either of the tension type or the one accompanied by profuse sputum, external drainage will oftentimes reduce the size of the cavity so that subsequent thoracoplasty is more effective and less extensive;

experiments may not be so in humans and vice versa To establish the validity of a human carcinogen requires clear cut statistical support, and even this may not be enough to satisfy those who are most critical. The relationship of pulmonary cancer to the smoking of tobacco is a case in point. Wynder & Graham (61) and Doll & Hill (62) have currently presented data of a very convincing sort indicating not only that bronchogenic carcinoma in humans is on the increase, but that it cannot be due entirely to improved diagnostic methods and that the rising incidence is associated with the smoking of cigarettes Doll & Hill cite that the death rate from lung cancer in England has increased six-fold for men and three-fold for women between the periods 1921 to 1930 and 1940 to 1944. This same precipitous rise has also occurred in many other countries. Of considerable importance is the fact that the increase has occurred during the past five years in the good teaching hospitals and to the same degree in both urban and country districts These facts seem to substantiate well the view that bronchogenic carcinoma is rising in incidence. Both of the above-mentioned studies have been well set up from a statistical point of view, and both show an undeniably strongly significant association between prolonged heavy smoking, of cigarettes in particular, and the occurrence of pulmonary cancer. Wynder & Graham observed that of 605 men with bronchial carcinoma, only 1.3 per cent were nonsmokers and 51.2 per cent had smoked more than 20 cigarettes a day for 20 years or more. In an adequate control group of general hospital patients, they found 14 6 per cent to be nonsmokers and only 19.1 per cent who smoked more than 20 cigarettes a day A similar contrast was observed between women with bronchial carcinoma and an adequate control group. The same picture was derived by Doll & Hill (62) from their very carefully worked out study of 649 men and 60 women with carcinoma of the lung The comments of Doll & Hill concerning the meaning of this statistical demonstration is best quoted:

> This is not necessarily to say that smoking causes carcinoma of the lung The association would occur if carcinoma of the lung caused people to smoke or if both attributes were end effects of a common cause. The habit of smoking was, however, invariably formed before the onset of the disease (as revealed by the production of symptoms) so that the disease cannot be held to have caused the habit, nor can we ourselves envisage any common cause likely to lead both to the development of the habit and to the development of the disease 20 to 50 years later. We therefore conclude that smoking is a factor, and an important factor, in the production of carcinoma of the lung

Further information reinforcing the above conclusions is to be found in a most interesting paper by Dungal (63), who reports a very low incidence of bronchogenic carcinoma in Iceland, only 2 9 per cent of all cancers there being bronchogenic carcinoma, in contrast to 20 per cent or more of this same type of tumor occurring in the United States and England The high rate in males as contrasted to females was found in Iceland as it has been in

chest wall. Dressler, Bronfin & Grow (55) report on the surgical experience and pre- and post-operative pulmonary function studies in nine cases so treated. In all these cases, the post-operative studies showed but slight diminution in breathing power and the surgical course, even in those patients having a severely crippled respiratory apparatus, was remarkably free of respiratory distress. These observations have been repeatedly confirmed in the reviewer's laboratory. This procedure, based on sound physiological principles, merits further use. The surgeons with whom the reviewer is associated perform the operation somewhat differently and remove the lucite spheres and overlying ribs several weeks after the first operation, by which time a firm chest wall has developed.

The problem of evaluating the rôle of pulmonary resection in the treatment of pulmonary tuberculosis has been complicated by the advent of streptomycin. Sweet (56) has reported a further follow-up of his original series of 63 patients who underwent extirpative surgery for pulmonary tuberculosis. Of the 54 who survived the operation, only 19 are reported as having remained continuously well, the other 35 having experienced subsequent reactivation. Some of these latter have since recovered. Of the 63 original patients, 26 are now reported as apparently well, 28 dead, and 9 alive but suffering from active disease. Sweet now considers only those cases unsuitable for thoracoplasty as being proper for resection, including of course those with a persistent cavity after an adequate thoracoplasty. These indications are generally accepted, as has been noted by Maier (57), with the added fact that the use of streptomycin coincident with the surgical procedure will definitely lessen the number of complications. It is generally known that other clinics are using considerably broader indications for pulmonary resection in the treatment of tuberculosis. The segmental resection of cavity bearing areas with or without coincident streptomycin is being studied by Chamberlain (58). Time alone will determine the proper indications. It might be said, perhaps somewhat facetiously, that if tuberculosis therapy runs its usual course of changing fashion, we will have a new technique before the present one has been adequately evaluated. Certainly one can say in regard to therapy for tuberculosis that it is no longer a cut and dried affair of bed rest, phrenic nerve crush, or pneumothorax. The need for an intimate knowledge of all aspects of the tuberculosis problem by physicians in general was never greater than it is today. An excellent review of current tuberculosis problems covering aspects not discussed in this review has been published by King (59).

Pulmonary Cancer

Hueper (60) has listed the known and suspected environmental carcinogens with a brief comment on their experimental and clinical status. This report was probably purposely made oversensitive to possible carcinogens, and the reader should also bear in mind that carcinogens effective in animal

experiments may not be so in humans and vice versa To establish the validity of a human carcinogen requires clear cut statistical support, and even this may not be enough to satisfy those who are most critical The relationship of pulmonary cancer to the smoking of tobacco is a case in point. Wynder & Graham (61) and Doll & Hill (62) have currently presented data of a very convincing sort indicating not only that bronchogenic carcinoma in humans is on the increase, but that it cannot be due entirely to improved diagnostic methods and that the rising incidence is associated with the smoking of cigarettes. Doll & Hill cite that the death rate from lung cancer in England has increased six-fold for men and three-fold for women between the periods 1921 to 1930 and 1940 to 1944. This same precipitous rise has also occurred in many other countries Of considerable importance is the fact that the increase has occurred during the past five years in the good teaching hospitals and to the same degree in both urban and country districts. These facts seem to substantiate well the view that bronchogenic carcinoma is rising in incidence Both of the above-mentioned studies have been well set up from a statistical point of view, and both show an undeniably strongly significant association between prolonged heavy smoking, of cigarettes in particular, and the occurrence of pulmonary cancer. Wynder & Graham observed that of 605 men with bronchial carcinoma, only 1.3 per cent were nonsmokers and 51.2 per cent had smoked more than 20 cigarettes a day for 20 years or more. In an adequate control group of general hospital patients, they found 14 6 per cent to be nonsmokers and only 19.1 per cent who smoked more than 20 cigarettes a day A similar contrast was observed between women with bronchial carcinoma and an adequate control group. The same picture was derived by Doll & Hill (62) from their very carefully worked out study of 649 men and 60 women with carcinoma of the lung. The comments of Doll & Hill concerning the meaning of this statistical demonstration is best quoted.

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all other countries. The consumption of tobacco, especially cigarettes, has been comparatively low in Iceland during the past 20 to 25 years but is now on the up grade The cancer statistics in Iceland in 1960 to 1965 will be of great interest.

Pulmonary resection for cancer of the lung has been an accepted procedure long enough to begin to analyze its results. Most surgeons report a very high percentage of the explored cases as being found to be inoperable (64, 65, 66). This indicates a need for better criteria whereby inoperability can be judged accurately prior to exploration In addition to the usual clinical evidences of extension beyond the operable stage, Dotter, Steinberg & Holman (67) have considered the use of angiography for collateral evidence. Of 53 cases of confirmed bronchial carcinoma studied by them, 22 were thought to present convincing angiocardiographic evidence of inoperability. Of these, eight were explored and all found to be inoperable. It appears that angiography has a role to play in conjunction with other methods for assessing operability, especially in those cases that cannot be definitely declared to be inoperable on some other basis. Of 158 operable cases, Rienhoff (64) reports 15 who have lived five years or more. Graham (65) reports a crude five-year survival rate of 28 per cent; in those with gland involvement, a survival rate of 15 per cent. Of operable cases, Overholt (66) reports a crude five year survival rate of 24 4 per cent and points out that the most favorable outcome is to be expected in those with no evidence of extension at operation and in those with epidermoid carcinoma. All authors note a longer period of survival in those resected as compared to those explored but not resected All also plead for early diagnosis and broader use of pulmonary exploration

The question of whether or not a space correcting thoracoplasty must be done to prevent the overdistention of the lung after lobectomy or pneumonectomy is of considerable practical importance, especially in resection for cancer or suppurative disease Following pneumonectomy or even lobectomy for tuberculosis, a space correcting operation is routine in almost all clinics because of the fear that overdistention will aggravate smoldering or inactive tuberculosis. Cournand *et al* (68) have observed that pneumonectomy is not inevitably followed by physiologic evidences of overdistention of the remaining lung. They believe that repeated observation at intervals of six weeks following the resection will afford evidence, in terms of progressive fall in the maximum breathing capacity and elevation of the residual air, that a space correcting thoracoplasty is needed. Cournand *et al.* (68) also observed that during exercise, pulmonary hypertension occurs in the pneumonectomized individual No evidence of right ventricular hypertrophy has developed in these persons, however, even though exercise privileges have not been restricted. Peters *et al* (69) have studied 10 children 8 months to 13 years after pneumonectomy without thoracoplasty. On the basis that one normal lung should exhibit physiologic measurements equivalent to 50 per

cent of a normal person, the only abnormality noted by these authors was that, after pneumonectomy, the remaining single lung was considerably enlarged and the residual air increased in some. The authors were impressed with the exercise tolerance of the pneumonectomized children. They stress the importance of physical exercise during the postoperative years. Neither of these studies answers the question of whether or not alveoli increase in number in the remaining lung after pneumonectomy, but they do indicate that routine thoracoplasty in nontuberculous cases is not warranted.

Bronchial Asthma

The advent of ACTH and cortisone has restimulated a general interest in bronchial asthma Numerous clinics are studying the effect of these two drugs on the asthmatic patient. Bordley *et al* (70) and Rose *et al.* (71) have treated cases of severe intractable asthma with ACTH The immediate results have been remarkably good. Four of the six patients treated by Rose had a complete remission of symptoms, and the other two experienced marked relief. The study by Rose *et al* is a nice example of applied knowledge These authors showed that histamine and mecholyl, which in the control period had been very effective, were both unable to depress respiratory function when administered during the treatment period. In addition, the inhalation of a grass extract which, prior to treatment, had caused a severe asthmatic seizure was not effective in this respect during ACTH therapy. Of considerable significance is the fact that the reaction to skin tests with allergens was unchanged in these patients. Rose *et al.* interpret their study as indicating that although the allergen-antibody reaction of asthma persists, the ACTH alters the histidine-histamine balance to reduce or neutralize the latter and, in addition, reduces the sensitivity of the bronchiolar musculature to such compounds as mecholyl or histamine It can be anticipated, as has been borne out by subsequent experience, that since the allergen-antibody reaction persists, the effects of ACTH or cortisone will not persist long after withdrawal of these drugs and that attacks of asthma will recur whenever the combination of provoking factors recurs

The many conditions that influence the development and character of an asthmatic attack are discussed by Abramson (72) The importance of the psychological factors is emphasized Abramson suggests that the psychological pattern is important not only from the viewpoint of psychotherapy per se but also from the standpoint of choice of drugs For example, in the hostile asthmatic, the sympathomimetic amines may be of far less value than sedation, whereas in some other types of personality, sedation must [illegible]

[illegible] very broad way is [illegible] 46 patients with bronchial asthma They believe the lymphoid and adrenal changes in status asthmaticus are evidence suggestive of "alarm reactions" secondary to

"alarming stimuli" such as histamine, epinephrine, hypoxia, and emotional stimuli. The long continued and repeated insults from these alarming stimuli, they believe, may account for the relatively high incidence of "diseases of adaptation" that were observed in their necropsy series. The fact that ACTH (71) is so effective adds weight to this viewpoint.

The attempt to cure or alleviate the symptoms of the medically refractory asthmatic patient by autonomic nerve section continues. Klassen *et al.* (74), Abbott *et al.* (75), and Blades *et al* (76) report additional studies The results can best be expressed in the words of Blades *et al.*: "These data demonstrate the bewildering consequences of an empirical approach" The reviewer would like to add that the data also indicate that more than one mechanism acts to produce that clinical picture which is termed bronchial asthma. The effects of bronchorrhea, mucosal edema, and bronchial spasm all are expressed as airway obstruction or asthma These three physiological phenomena can occur as the result of local stimulation without nerve pathway involvement or may arise as the result of remote stimulation via the autonomic nervous system (especially the vagi). When one considers the local, humeral, and nervous mechanisms that may initiate an attack of asthma, there is little reason to wonder that denervation leads to such diverse end results. These three papers warrant far more discussion than can be entered into here, not because of the clinical end results, which were very conflicting, but because of the numerous interesting speculations that might be derived therefrom.

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PHYSICAL AGENTS AND TRAUMA

Trauma due to Stress and Physical Agents[1]

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INTRODUCTION

The purpose of this chapter is to provide physicians with authorative references concerning the traumatic state induced by a variety of physical agents and conditions The attempt will be made to outline (*a*) interrelationships and common pathologic and functional derangements induced by various agents, (*b*) tolerance limits and the range of compensation or adaptation in the face of the operative stress prior to injury, and (*c*) preventive and therapeutic measures

The authorative summaries and reviews of various military stresses and the action of traumatic agents as incorporated in such compilations as *Advances in Military Medicine* (174) prepared by the National Research Council provide a wealth of material from which only a few salient points are enumerated.

In preparing this material the reviewer is impressed by (*a*) the amazing ability of the body to withstand crash injury trauma if acting forces are distributed over large areas and the wide range over which various stresses are tolerated, provided adaptation is affected, (*b*) the importance of environmental and body temperatures under various conditions of peripheral injury, such as in the case of burns, to eliminate pain, decrease absorption of toxic materials, and delay the onset or minimize the severity of the shock state, (*c*) the simplicity of certain procedures as the backward facing of seats in aircraft, and (*d*) the promise that cold therapy holds in burns and other types of injury.

The physician is pre-eminently in a position to exercise a paramount role leading to the employment of preventive measures to reduce many of the tragic and gruesome disabilities that take their greatest toll during the chief productive period of life. The body's reaction may be considered first in relation to some simple types of stress not usually considered to be productive of injury

INTERRUPTION OF DIURNAL RHYTHMS

The work of Kleitman (1) emphasized the fatigue producing effects of continually changing work-sleep routines Man has relatively fixed physiological rhythms, such as the diurnal temperature cycle which is not readily

[1] This review covers approximately the period from September, 1949 to September, 1950

changeable. When these rhythms are not in synchrony with his sleeping and waking cycle, it is probable that his efficiency and his feeling of well-being are reduced and his rest disturbed. The practice of rotating watches disregards this fact. The elimination, for example, of the diurnal temperature rhythm by a rotating Navy watch-stander's schedule was demonstrated most convincingly by Utterbach & Ludwig (2) who continued an investigation initiated by Kleitman Some two to three weeks are required for a new dirunal rhythm to establish itself. This simple type of stress, although easily obviated by constant work-sleep routine, operates to reduce efficiency and promote fatigue Data are accumulating to indicate that maximal efficiency tends to coincide with temperature peaks, and there are data indicating that circulation may be more efficient in the afternoon (high temperature) than in the morning (low temperature)

STRESS DUE TO OBESITY

Excess fat is an obvious traumatic agent and is associated with shortened life expectancy and a higher incidence of cardiovascular disease and diabetes [Dublin, Lotka & Spiegelman (3)]. The reduction of excess body fat through dietary measures is simple in concept, but to ascertain the optimal weight for a given individual, taking into account body type, age, and hormonal factors, is the more complicated crux of the problem What is the underlying mechanism, for example, that permits one individual to eat to satiety and remain lean while another "grows fat"? Insight into this problem is afforded by studies that permit the accurate determination *in vivo* of fat content.

For healthy young men, it was possible for Behnke, Feen & Welham (4) to determine body volume according to Archimedes principle and, hence, values for specific gravity as a whole The fat content of the body was found by Rathbun & Pace (5), in analyses on guinea pigs, to vary inversely with specific gravity, a value of 1 100 denoting leaness and one of 1 020, a fat content of about 40 per cent of the total body weight

If fat is the chief variable effecting body density, it follows that there must be a lean body mass (specific gravity 1 100) of uniform composition, least in regard to such major components as water Data on various mammalian species indicate that 72 to 73 per cent of the lean body mass is water [Pace & Rathbun (6)]. Any decrease in the percentage of body water in relation to total weight from a level of 72 to 73 should permit accurate estimates of fat content It was an important clinical contribution, therefore, when Soberman *et al* (7) developed an accurate method for the measurement of total body water using antipyrine. Recently, this method has been simplified by Berger *et al* (8) Messinger & Steele (9) and then Osserman and co-workers (10) showed that the clinically feasible method for estimating body fat content on the basis of antipyrine determinations showed a high correlation with fat estimates based on determinations of specific gravity.

Pertinent to our problem, however, is that fact that not only on several groups of men between the ages of 20 and 40, but also in other mammalian

species, the values for specific gravity range between 1.020 to 1.100. That normal individuals of different species have values for body fat ranging from values approaching zero to 40 per cent of the total body weight constitutes a riddle of metabolism that must be solved in order to determine what constitutes optimal body weight for any given individual. Enforced hunger, as in Europe, resulted in large losses of excess fat in normal individuals, but ad lib. eating again tended to restore the lost fat and previous body weights. The leanness was not maintained, and well-being for the heavy individuals was associated not with lean but rather with an obese condition.

EFFECT OF RELATIVE INACTIVITY AND OF ABNORMAL MOTION

Bed Rest

The debilitating effects of bed rest per se continue to be evaluated on a quantitative biochemical and physiologic basis. Taylor *et al.* (11) showed that bed rest in healthy men was associated with a loss in cardiovascular function, a decrease in heart volume of 17 per cent, and an increase of resting and exercise pulse rates There was marked deterioration in cardiovascular responses to posture.

Motion Sickness

An enormous amount of time and energy was spent studying motion sickness during and following World War II, and résumés of the investigations are given by Bard (12) and by Tyler & Bard (13). Motion sickness represents a serious incapacitation produced by a stress which affects primarily a single organ system No normal person is immune, and about 10 per cent of all adult individuals are highly susceptible The agreement is general that hyoscine in a dose of 0 6 to 0 8 mg protects from 50 to 60 per cent of susceptibles over a period of at least a half hour without producing side effects undesirable from a military point of view.

Dimenhydrinate vs hyoscine.—Both drugs appear to be about equally effective in the prevention of motion sickness During the initial enthusiastic periods attending the introduction of dimenhydrinate (Dramamine), Tyler (14) called attention to the need for controlled tests employing hysocine as well as a placebo The tests of Strickland & Hahn (15) and Simon & Seyler (16), representative of this type of study, indicated that dimenhydrinate reduced motion sickness about 50 per cent or to about the same degree as hyoscine In passengers, the drowsiness produced by dimenhydrinate may be desirable; in military personnel, this effect on about 10 to 25 per cent of individuals is of course undesirable

Shaw (17), reviewing tests conducted in the U. S. Navy, concluded that dimenhydrinate was prophylactic against motion sickness in 50 mg. doses and that it was effective as a therapeutic agent in 100 mg doses The larger dosage produced drowsiness in 25 per cent of individuals In the excellent report by Boland & Grinsted (18), it was concluded that scopolamine and

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dimenhydrinate were equally effective in the prevention and ultimate cure of air sickness. Side effects reported were few, mild, and similar for both types of medication. One of the many valuable contributions of Wendt (19) in the field of motion sickness is his evaluation of the psychological factors involved, a study applicable not only to motion sickness but affording insight into the psychic effects of other stresses as well.

Changes of Acceleration

One of the chief problems of aviation medicine, protection against high accelerative forces, suggests the difficulties confronting the physiologist in altering, for example, a homeostatic circulatory arrangement that evolved in an environment of relatively slow motion. Concern over this problem is evident as early as the forties of the last century when the first railroad was built. A committee of physicians published a statement which claimed that the human body would not be able to stand the anticipated speed of 25 m.p.h. [Gauer *et al.* (20)]. Rapid change of acceleration, no doubt, was considered rather than acceleration.

In 1950, aircraft were travelling at sonic speeds which exceeded by more than threefold the conduction of nerve impulses. The tremendous strain on the cardiovascular system is evident from statements by Landis (21). An airplane travelling at 400 m.p.h. and turning in a radius of one-quarter mile develops some 8 *g*, and the pilot (weight, 180 lbs) will press on his seat with a weight of 1,450 lb. The effective specific gravity of his blood will be well over that of mercury, and the hydrostatic pressure of blood in the region of the ankles will be over 650 mm. Hg in addition to the arterial pressure due to heart action. Loss of fluid from the vascular system by filtration during a period of 5 min. exposure at 3.5 to 5 *g* amounts to some 250 cc. This fluid is reabsorbed rapidly during rest periods between exposures.

Tolerance values—In the inside loop (plus *g*) with the pilot in the conventional position, there occur changes in ear opacity, disappearance of ear pulse, blackout, and semiconsciousness These symptoms are associated with falling arterial pressure at the head level and consequent progressive failure of circulation and hypoxia in retina and brain Gagge & Shaw (22) and Lombard (23) have plotted data on *g* tolerance in relation to the time factor which is bound inextricably with the magnitude of force in production of symptoms. Three to five *g* over a period of several seconds is associated with blackout while 6 *g* will result in loss of consciousness This is estimated as one-tenth to one-fiftieth of the lethal force (21) There has been no organic damage reported in vigorous adults blacked-out many times The ingenious experiments of Lambert (24) demonstrate the relationship of retinal ischemia to blackout. By neutralizing the effect of intraocular pressure with suction cups applied to the eye, it was possible to raise the blackout threshold so that it corresponded with that of loss of consciousness The tolerance for negative acceleration (outside loop, force exerted from feet to head) is much less than that for positive acceleration. Disagreeable symptoms as a sensa-

tion of eyes being pushed out, "redout," mental confusion, and motor incoordination are associated with 2 to 3 plus g. Gamble and co-workers (25) concluded that cerebral symptoms occurring at levels of headward centrifugal force in the range of 3 to 5 g may be due to the marked carotid sinus stimulation that accompanies the increase in blood pressure at head level. Tolerance for changes in acceleration is adversely affected by warm environments and by minor infections, gastroenteritis, and excessive fatigue.

Protection.—Abdominal support alone is inadequate, affording some 0 5 g protection. With the lower extremities pressurized, the protection is increased to about 1 5 g.

VIBRATION

Davis (26) points out that there is continuity between the problems of vibration and those of acceleration (Table I). In the lower frequencies, the whole body is affected; with higher frequencies, a particular small area may be involved, as the ear. With the highest frequencies, there occurs disruption of specific cells, and the effect may even be specific for large molecules

Ultrasonic vibrations—The term "ultrasonics" refers to vibrations of the same general character as sound waves but of frequencies above 20,000 cycles, inaudible to the human ear A publication by Bergmann (27) containing some 2,000 references is devoted to the physical aspects of ultrasonics The biological effects have been extensively studied by Harvey (28). The role of ultrasonics in medicine was the subject of a congress held in Erlangen in 1949 (29). The military services are furthering physical and biological studies headed by Goldman at the Naval Medical Research Institute and Parrack at Wright Field

The basic physics of ultrasonics is under investigation by Schilling at Pennsylvania State College. In the Department of Physiology and Biophysics at the University of Washington, L H. Carlson and his co-workers are interested in the coagulative effects of ultrasound on tumors Ludwig & Struthers (30) have outlined the considerations underlying the use of ultrasonics to detect gallstones and foreign bodies in tissues.

The disturbing reports of various types of symptoms experienced by workers in the vicinity of jet aircraft test stands do not appear to have any physiologic basis In guinea pigs exposed four hours daily to the noise of jet turbo engines, Wilcox & Windle (31) found destruction of the organ of Corti but no other neurological changes. Reports, however, of the therapeutic value of the vibrations emanating mainly from Europe require some evaluation of this type of energy.

Gregg (32) outlines the physical and biologic action of ultrasonic vibrations

Review of the work on the biologic effects of ultrasound indicates that most of the observed effects may be classified as being due either to cavitation in the presence of dissolved gases or to conversion of acoustic energy to heat energy (absorption) How-

TABLE 1

THE RELATIONSHIP BETWEEN LEVELS OF VIBRATION FREQUENCY AND BIOLOGICAL EFFECTS*

Stimuli	Biological Effects
g Forces	Problems of the circulatory system
Alternating Motion (Slow Movement)	Motion sickness: As related to labyrinthine, visceral, and perhaps visual stimulation.
Lower Range of Frequency	Effects on proprioceptor system (sense organs of kinesthetic sense): Fatigue of the proprioceptor system may have an important influence on performance
Next Higher Range of Frequency	Tactile effects: Stimulation of skin receptors
Range of 20 to 10,000 Cycles with Intensity of 120 to 130 Decibels	Effects on hearing: Blanking out of auditory system may occur such as results when working in the presence of loud noise
Middle or Lower Part of Auditory Range	Visual effects. There are certain frequencies specific for the eyeball which will most readily produce blurred vision when the head is exposed to stimuli of this order
140 Decibels	Painful effects The ears are first affected at this level The pain threshold presents a flat curve. Protection to the ears may be accomplished by means of simple ear plugs.
Slightly Higher Intensity	Lethal effects on bacteria: This has resulted commercially in a means for pasteurization of milk.
Frequency, 10,000; Intensity, 150 to 156 Decibels	It is possible that olfactory effects may be encountered
Next Higher Range of Frequency and Intensity	Thermal effects: The hand placed in such a sound field will be warmed between the fingers, pain may result, and blisters may form
	If the body reflects all the energy, no thermal effects will be encountered. However, if the system absorbs the energy, it will be heated When the energy is of a sufficient degree, thermal problems result Also, the energy may be of such intensity as to tear a system or an organ apart.
Next Higher Frequency above That of Sound	Cavitation The creation of a vacuum occurs when the cohesive force of liquids breaks down. At this same level, colloids can even be dispersed Mercury can be emulsified in water

* From Davis (26)

ever, the former leads to production of high local temperatures, local electrical potentials, intense agitation and secondary chemical reactions, and the exact role played by each of these secondary effects has yet to be evaluated by further investigation.

Changes in the structure of cells (spirogyra) have been reported by Lepeschkin & Goldman (33). Ultrasound therapy is reported in Europe as being beneficial for a variety of diseases. Nelson, Herrick & Krusen (34), in their classical paper, have summarized the present status of ultrasonic therapy

The destruction of malignant tissue is attributed to the high local temperatures (Carlson). An advantage over therapy with x-ray is that focussed ultrasonic irradiation may possibly avoid the over-all destructiveness of x-rays Lynn & Putnam (35) produced small cerebral lesions in animals by focussed ultrasound at 835 kc

In an experimental study, Baldes, Nelson & Herrick (36) were able to produce high temperatures in bone marrow and bone with relatively low outputs of energy. Adjacent tissues were heated only moderately. Temperatures produced in bone and bone marrow may rise to dangerous levels within a few minutes

In conclusion it appears that ultrasonic vibrations have established industrial applications (homogenization of milk) In diagnosis and therapy, there are insufficient data available to evaluate their usefulness. At present, they constitute a means of diathermy for the induction of high localized temperatures

INJURIES DUE TO MISSILES

Medical and surgical problems of warfare again come up for consideration. The experiments in the field of wound ballistics of Harvey and his coworkers (37), continued by investigations in the Medical Division of the Army Chemical Center, clarify the manner in which shock waves associated with the passage of a bullet through tissue produce in addition to the injury of the direct hit (*a*) hemorrhage of the lungs, (*b*) perforation of the intestine, (*c*) splitting of muscles along fascial planes, (*d*) cracking of a long bone, (*e*) loss of nerve function without external injury, and (*f*) the disintegration of a large mass of tissue under the skin despite a small entrance and exit hole.

The war collection of the Royal College of Surgeons described by Gordon-Taylor (38) contains material illustrating the variety of injuries produced by missiles With reference to the heart, mention is made of the principle of not removing foreign bodies if they do not produce symptoms or signs of dysfunction

Protection —In World War II, the anachronism of aviators in body armor was associated in the Eighth Air Force with an 80 per cent reduction in casualties that otherwise occured from high velocity fragments.

INJURIES DUE TO BLAST

War experiences showed that air blast in contrast with underwater

blast caused little disability. In the classic review by Clemedson (39), much of our knowledge of the effects of air blast is summarized. Worthy of mention is the capacity of solid tissues to withstand injury in contrast with the susceptibility of tissues adjacent to air or gas media as lungs and hollow viscera. Greaves *et al* (40) investigated the serious pulmonary and abdominal injuries associated with underwater blast and emphasized the danger of hemorrhage and perforation in viscera containing gas. Protection against air and underwater blast waves is provided effectively by abdominal and thoracic shielding The life jacket was especially effective against pulmonary injury.

INJURIES DUE TO IMPACT FORCES

Investigations into the prevention of injury afford the greatest promise of reducing the tremendous disability and loss of life brought about by carelessness and disregard for safety.

Statistics.—Dublin, Lotka & Spiegelman (3) state that the human life wasted by accidents is surely capable of material reduction. If these fatalities could have been eliminated in 1939 to 41, the average length of life of white males would have been increased by 1.9 years. Among white males, accident fatalities cost more lives than cancer. Nearly 40 per cent of all deaths below 19 years of age are due to accidents

In the military service, 3 out of every 1,000 men are rendered ineffective (noneffective ratio) by accidents compared with 25 ineffective from disease [Ware (41)] This value is remarkably stable from year to year (42) and for various branches of the service.

With reference to motor vehicle accidents, some 30,000 to 35,000 people are killed each year and about one million people injured. The economic loss also from these accidents is of the order of 2 5 billion dollars. Some 20 per cent of deaths between the ages of 20 and 50 are due to motor vehicle accidents.

Tolerance of the body as a whole and of individual tissues.—It becomes apparent from the analyses of De Haven (43, 44) and the experiments of Stapp and co-workers (45) that the body is capable of withstanding tremendous forces if local deformation of tissues does not occur in vital areas Falls of individuals from heights of 140 ft have been recorded without serious injury, and miraculous escapes from injury have occurred in demolishing airplane accidents where individuals were protected from contact with surrounding structures or when the impacts were distributed over relatively wide areas and some of the impact force absorbed by protective materials. In a major aircraft disaster at Cardiff, Wales, head injury from acute jackknifing such that the head struck not the upper back of the seat forward but the lower support of the forward seat was the almost invariable cause of death. The Air Force test team headed by Stapp have overcome major obstacles to provide elaborate equipment [Denzin (46)] and instrumentation required for studies of human tolerance in crash deceleration.

The results of a preliminary series of brilliantly conceived experiments of far reaching importance indicate that the human body can be subjected to about 35 g for 0 12 sec injury; jolt loads of 58 g have been recorded on safety belts and shoulder harness during the tests Under these conditions, a 154 lb. subject sustained an average force of 5,450 lb for 0 12 sec. and more than 8,700 lb. for 0 01 sec. or 21 and 34 lb per sq in , respectively. One of Stapp's subjects sustained 20 test runs and two others, 13 runs each in both forward and backward seated positions with no evidence of accumulative effects.

Beginning at about 35 "g" average, mild circulatory shock of short duration could be observed in most subjects One subject sustained a fracture of the tips of the left tenth costal cartilage while undergoing 11 "g" deceleration with an inadequate harness. The same subject sustained a fracture into the wrist joint when his hand slipped during a 38 1 "g" deceleration.

The only other injuries were muscle soreness and bruises An appreciation of the magnitude of the forces operating under the test conditions is gained from the fact that an unrestrained dummy weighing 185 lb. came to rest 700 ft. from the point where the test sled stopped after having passed through a one-inch pine board panel De Haven's generalization is re-emphasized, namely, that the strength of aircraft structures and installations rather than the strength of the human body is the limiting factor in personnel protection

In regard to individual tissues and specific body areas, Carothers, Smith & Calabrisi (47) and Evans & Lebow (48) have measured the elasticity and strength of certain long bones of the human body. Compression forces on the whole femur were about 2,000 lb before fracture occurred (47). The abdomen, which might be considered vulnerable, actually tolerates without serious injury large forces of the order of 4,000 lb. In crashes of light airplanes, it has been found that safety belts capable of resisting breakage up to 4,000 lb and restraining an area of 20 sq in at the hips have been broken in crashes without apparent injury at the site of restraint or elsewhere [Wurzel, Polansky & Metcalfe (49), De Haven (50)]

Areas most frequently injured—The parts of the body most injured most frequently in percentage terms are: head, 49, leg, 20; arm, 14; spine, 10, chest, 7; pelvis, 4; scrotum, 4; abdomen, 2 [Du Bois (51)]

Personal protective measures.—The most important lifesaving and protective measure in aviation, namely, restraint of aviators by shoulder harness gear to prevent contact with surrounding structures, was introduced years ago by former Air Surgeon Major General Malcolm Grow. Bierman, Wilder & Hellems (52) reported on the principles of protection of the human body as applied in a restraining harness for aircraft pilots. The limits of body tolerance for fixation and restraint under crash conditions in contrast with the employment of energy absorbing materials which stretch and allow the body to move out of position remains to be determined It is one of the problems under study by Commander E M. Wurzell of the Naval Medical

Research Institute The factor limiting fixation is the possibility, not of external injury, but of displacement, distortion, and rupture of internal organs and blood vessels [Rushmer (53)].

Changes in aircraft design.—Only the simple innovation initiated and furthered by Pekarek (54) will be mentioned, namely the backward facing of seats. With adequate seat fixation, the support afforded the back of the body against crash impact is the simplest measure to afford maximal protection Passenger view and comfort are increased by this measure. Failure or tardiness in making this change illustrates the great engineering and commercial barrier that the physiologist must overcome even though general agreement exists that his recommendation is scientifically sound, mechanically feasible, and generally desirable

TRAUMA INDUCED BY ALTERATIONS OF BAROMETRIC PRESSURE

High Altitude Residence

Anoxia.—The ability of human beings to adapt to a constantly operating stress is demonstrated convincingly by the ability of the Peruvian Indian to perform hard work at altitudes of 14,000 to 16,000 ft. At the International Symposium on High Altitude Biology, Lima, Peru, November 23 to 30, 1949, it was possible to experience the incapacitation of the newcomer at an altitude of 14,500 ft. and at the same time watch Indians engage in a strenuous game of football. The studies of Monge (55), Hurtado, Rotta, and certain other members of the Institute of Andean Biology and of Van Liere (56) elucidate the remarkable acclimatization to altitude and striking physical differences between the Andean and the dweller at sea level, e g, (*a*) absence of excess fat, (*b*) increased vital capacity, and (*c*) increased red blood cells and hemoglobin (up to 25 per cent) Evidence of hormonal changes and hypertrophy of glandular tissue in contrast to the effects of acute anoxia are not observed. Subtle biochemical tissue and cellular adjustments are under study.

In the breakdown of acclimatization to high altitude [Monge (55)], the compensatory polycythemia of the adapted individual becomes polycythemia vera with red blood cell values of 6 5 to 8 5 million. The lungs become emphysematous, the pulmonary vessels undergo sclerotic changes, and the right side of the heart becomes enlarged with abnormalities recorded in the electrocardiogram

Acute anoxia.—In contrast to the native resident, the newcomer does not have the capacity for work, his immediate adjustments are primarily respiratory and circulatory The respiratory alkalosis and disturbed sleep are well known The most striking findings, however, relate to altered glandular morphology and function in lower animals subjected, admittedly, to a severe condition of anoxia. These may be eumerated as (*a*) enlargement principally of the adrenal cortex, (*b*) increase secretion of epinephrine, (*c*)

increase in blood sugar, (*d*) reversible decrease in thyroid function equivalent to a surgical thyroidectomy [Van Middlesworth (57)], (*e*) decreased gastric motility, (*f*) loss of fertility, degeneration of spermatogenic cells, and (*g*) hemorrhages in the intestines and other organs.

In the experiments of Altland (58) and Highman & Altland (59), the hemorrhages into the intestine and other organs and sterility of rats, exposed daily to simulated altitudes of 25,000 ft., are also pathologic derangements of radiation sickness. One of the most significant findings of Altland and his co-workers is that bacterial endocarditis may be readily induced in rats exposed 4 hr daily to a simulated altitude of 25,000 ft.

Artificial acclimatization—Several months of residence at altitude are required for the newcomer to become partially acclimatized, but even after six months in contrast with heat stress he has not adapted as completely as the native, based on values of hemoglobin and acid-base equilibria. Exposure in a low pressure chamber for a period of one month likewise fails to induce the degree of acclimatization enjoyed by the native [Hurtado (60)]. Evidence that some degree of acclimatization can occur in short daily exposures or that acclimatization once acquired can be maintained by short exposures in a low pressure chamber is of practical significance in the case of Andean pilots and military personnel. One of the most interesting experiments to create rapid acclimatization was the infusion of red blood cells in healthy men by Pace *et al.* (61) The normal value of hemoglobin was increased by some 22 per cent by the infusion of 1,000 cc of red blood cells without any ill effects. Partial acclimatization was evident from the lowered pulse in response to exercise under conditions of partial anoxia

Aviation Medicine

Attention is invited to the reviews of Gagge & Shaw, (22) Bronk (62), Whittingham (63), and Fulton (64) The traumatic effect of altitude changes on the ear and sometimes sinuses and teeth are problems occasionally confronting the physician About 1 to 2 per cent of flying personnel have difficulty sufficient to visit a physician, but some 25 per cent of individuals show barotraumatic changes in the tympanic membrane if the rate of exchange is sufficiently rapid as in exposure to high pressure. Dickson (65) reviews the Royal Air Force experience Pain and temporary loss of hearing are familiar phenomena The writer's observation of many men exposed to barotrauma in underwater operations is that permanent loss of hearing is not induced by this type of injury despite the extensive damage to the middle ear. Therapy of the chronic tubal obstruction, heretofore rather futile, became effective by the use of radium applications by Crowe & Baylor (66) and Crowe & Burnam (67)

Medical fitness for air travel.—Whittingham, Barbour & MacGown (68) provide a comprehensive, detailed outline on the medical contraindications to air travel. The number of deaths occurring within 48 hr after flight as well as those in flight should be determined. With reference to the cardiovascular

system, Graybiel's conclusions (69), are helpful. He states that there are few cases of circulatory failure observed in flight in commercial airlines and negligible difficulties involved in the transport of cardiovascular cases by the military, and he suggests that the practicing physician should keep the following in mind: (*a*) patients with congestive failure or a severe degree of coronary insufficiency should not be allowed to fly unless accepted as a calculated risk, and (*b*) cardiac patients with a moderate to great decrease in reserve should not be allowed to fly if it is anticipated that they will become overanxious during flight or develop motion sickness

Pressure breathing.—The investigations of Henry *et al.* (70) on the decrease in effective blood volume during pressure breathing and the use of counterpressurization of the limbs to minimize fluid loss, are of considerable clinical interest.

Effect of High Pressures—Decompression Sickness

Reviews of the physiological and pathological factors underlying decompression sickness have been prepared by Fulton (71), Catchpole & Gersh (72), Hoff (73), and Behnke (74, 75). The basic principles underlying the uptake and elimination of molecular nitrogen and other inert gases have been outlined by Smith & Morales (76) and extensive measurements have been made by Jones (77) and others The determination of cerebral blood flow by Kety (78) using nitrous oxide and of blood flow to individual organs on the basis of inert gas absorption and elimination [Jones (77)] including the use of radioisotopes have advanced to the stage of clinical application. Age is shown to be an important factor in gas uptake and elimination by the meticulous carbon monoxide experiments of Pace (79), by the nitrogen measurements and in decompression tests Estimates of pulmonary function on the basis of nitrogen clearance time from the lungs by Boothby (80) provide a simple clinical method of determining early emphysema and other impairment. The development of a new metabolism apparatus by Donald & Christie, not only for metabolism gas exchange, but for estimates of inert gas absorption and elimination for short periods, constitutes an important clinical advance

The inhalation of oxygen at high pressures promotes a rapid elimination of carbon monoxide from the blood as demonstrated by Pace, Strajman & Walker (81). The similarity of convulsive seizures induced by oxygen at high pressure to those of idiopathic epilepsy are indicated by the electroencephalographic studies of Stein *et al.* (82).

A therapeutic outline developed by medical officers in the Navy during the past 10 years has been especially effective with reference to decompression sickness The writer desires to emphasize the clinical value of an early sign of the presence of gas bubbles in pulmonary vessels, namely, a sensation of substernal distress on deep inspiration which frequently elicits the cough reflex particularly when tobacco smoke is inhaled. The symptoms produced by gas bubbles in blood and other tissues may be of limited interest

clinically but are of broad interest in experimental medicine. The simulation of many disease states by embolic interference with blood flow, and the reversibility of the induced changes by decompression, merits extended study. The production of a shock state induced without tissue trauma in which capillary stasis, hemoconcentration, and fall in blood pressure are related solely to the early reversible impairment produced by gas bubbles, is worthy of re-examination by clinical investigators Although the writer and others have ascribed the signs and symptoms of decompression sickness to intravascular rather than to extravascular bubbles, a healthy contrary view has been expressed by Ferris *et al* (83), and some corroborating experimental data have been furnished by Lund & Lawrence (84).

INFLUENCE OF WEATHER AND CLIMATE ON MAN

To the observations of the pioneers, Huntington (85), Petersen (86), and Mills (87), have been added a tremendous amount of precise clinical and physiological data pertaining to the effects of climate and especially the temperature environment Competent investigators in laboratories, such as the Quartermaster Climatic Research Laboratory at Lawrence, Massachusetts, have had the opportunity to observe and study large groups of men under conditions ranging from desert and tropical heat to arctic cold.

Clinically, the study of environmental temperatures is furthered by the type of investigations that are possible at the University of Illinois where superb facilities exist for the study of both the patient and normal individual under conditions of a controlled environment. The Quartermaster Corps of the United States Army have made extensive contributions in outlining clothing requirements for the inhabitable regions of the world It may be commented on that three groups of individuals are involved for the most part in the field of climatology and temperature control, namely, physicists, physiologists, and clinicians Few people understand the physicist's complicated mathematical and graphic representations, while the clinician's efforts are suppressed as empirical The physiologist on the basis of well conceived and controlled experiments speaks with assurance and admittedly bridges the gap between physicist and clinician He, in turn, however, is confronted by the broad information of the geographer and climatologist that natives, for example, live practically unclothed in Patagonia under cold conditions that are irreconcilable with the comparatively mild laboratory conditions The notable advances in the field, however, require the participation of these groups as well as the broadly trained geographers and climatologists The book edited by Newburgh on temperature regulation and science of clothing (88) summarizes ably the aforementioned advances and diverse approaches Additional excellent reviews and reference papers have been prepared by Lee (89) on climatology and tropical settlement, by Du Bois (90) on fever and the regulation of body temperature, and by Field & Hall (91), Hemingway (92), Kreyberg (93), and Hardy (94) on the effects of heat and cold. The annual handbook of the American Society of Heating and Ventilating

Engineers (95) contains chapters on physiologic principles and therapeutic applications as well as additional information helpful to physicians A much needed publication, *Thermal Standards in Industry*, has been prepared by the Committee on Atmospheric Comfort under the chairmanship of Yaglou (96).

Effects of Low Temperatures

Cold was by far the most disabling stress in World War II, and in the various armies, it incapacitated several hundred thousand men As in the Napoleonic campaigns, cold disrupted and brought to a virtual standstill the German advances in Russia In the Eighth Air Force, as high as 20 per cent of air raid personnel on numerous missions were rendered casualties by cold. Exposure to both wet and dry cold, not only of ground troops but also of aviators and survivors on life rafts, emphasized the importance of protective clothing and other measures in the care particularly of the hands and feet

Herrington (97) aptly points out that impetus to investigations of the effects of low temperatures was supplied before the war by the recognition that regions of the body with lowered temperatures were less susceptible to the development of malignancy, that certain embryonal cells were injured by temperatures below 35°C., and by the large number of experiments in which the temperature of the body as a whole was lowered by as much as 14°C.

The employment of low temperatures as a means of local anesthesia and therapy is established, and the advantages, as outlined by Allen (98), have been confirmed by Large (99) and others The control of environmental and body temperatures in the therapy of burns and certain types of shock with the consequent physiological isolation of the periphery or surface of the body by reduced blood flow, as demonstrated by immersion experiments in cold water, constitute for this reviewer the chief stimulus for the preparation of these notes

Cold tolerance and physiological changes of the body as a whole.—In contrast with high temperatures, the body can tolerate unbelievably low temperatures, the critical value for lethal body temperature being approximately 25°C [Herrington (97)] A fall in temperature from 39° to 35°C is associated with shivering, increased oxygen consumption, bradycardia, and retention of consciousness From 35° to 30°C, shivering ceases, there is a linear fall in oxygen consumption and loss of consciousness From 30° to 25°C, there occur cardiac decompensation and failure The sequence of events leading to cardiac decompensation and failure as given by Hegnauer *et al* (100) are (*a*) prolongation of the activity phase of the cardiac cycle, (*b*) decline in arterial pressure, and (*c*) increase in blood viscosity and a depression of cellular (heart) oxidations Measures to keep the heart warm prolong life and enable the body to withstand lower temperatures.

In human immersion experiments (water temperatures 43° to 50°F.,

i e., 6° to 10°C), Behnke & Yaglou (101) noted the well tolerated fall of body temperatures of 3 to 4°F. in the course of an hour associated with as much as six-fold increase in oxygen consumption due to shivering. After removal from cold water, deep body temperature fell an additional 4°F. during a period of 20 min. unless an immediate rewarming was effected in water 104°F. (40°C.). This fall in temperature is attributed to an equilibration of deep body and peripheral temperatures occasioned by the release of circulation into the previous constricted periphery The maintenance of good muscular function and deep body temperatures of 96° to 99°F. (35 5° to 37.2°C) in association with peripheral temperatures of 45° to 55°F (7° to 13°C) indicates the remarkable isolation for appreciable periods of time of core from peripheral tissues No injury except persistent paresthesia in the toes (water 43°F but not 50°F. for 1 hr.) occurred in these experiments It is of interest that the partial shift in blood flow from the core to the periphery is reflected by changes in the size of the liver and pulmonary vessels as observed by x-ray studies of Glaser, Berridge & Prior (102)

Hands and feet—The tolerance to cold of hands and feet depends to a large extent upon the deep temperature of the body which, if maintained, permits useful function at temperatures otherwise incapacitating [Rapaport *et al.* (103)]. Under these conditions, a skin temperature of about 50°F (10°C) is the lower limit for the maintenance of a reasonable degree of manual dexterity Men living continually for one month in cold environments, in experiments conducted by Spealman (104), were able to tolerate surface temperatures of the feet of approximately 63°F. (17°C) Acclimatization was indicated by the fact that the subjects became less and less uncomfortable and cyanosis disappeared

Physiologic facts of great significance are the reduced blood flow to cooled hands and feet by local cooling to 59 to 68°F. (15 to 20°C) when the body temperature as a whole is maintained and the great increase in blood flow (plethysmographic recordings) at water temperatures of 41 to 50°F. (5 to 10°C), equal to the flow at water temperatures of 86°F (35°C). The increased blood flow at low temperatures may be through arteriovenous anastomoses and essentially a reaction to injury. Brown *et al* (105), using a pressure type plethysmograph, record tissue edema rather than increased blood flow at 50°F (10°C) In view of clinical applications, it is of prime importance to determine the vascular reactions and oxygen supply in cooled tissues

Pertinent to the problem is the finding of Mead & Bader (106) that the cooling curve of the fingers is like that of the avascular finger, indicating the extent of activity of the arteriovenous shunts and other mechanisms which come into play In another report, Bader & Mead (107) state the important conclusion that blood flow through the fingers depends primarily upon the over-all body need to conserve or dissipate heat and that local rewarming of the cold digit is ineffective for re-establishing a high blood flow

Important adaptation responses relate to the adrenal gland [Stein *et al*

(108)] and the important role played by vitamin C. Therien & Dugal (109), in one of a series of excellent papers, reported a retention of ascorbic acid in tissues of rats exposed to a cold environment and a consequent preventive effect on adrenal hypertrophy

Cold injury.—Man appears to be the most susceptible of various species to cold injury [Brown & Landis (110)]. Especially resistant are cold blooded species. In cooling the frog mesentery, no signs of capillary injury or leakage of protein from capillaries appeared until after the tissue had been frozen. Lange, Weiner & Boyd (111) were able to produce a constant lesion in rabbits comparable to immersion foot. The lesions differed basically from frostbite mainly in that disturbances of nervous function and intravascular agglutination, phenomena characteristic of frostbite, were missing. The distinction between the types of injury produced by cold short of freezing and those following freezing is borne out by many studies and clinical observations pointing to the late occurrence of edema, the greater increase in capillary permeability, and the gangrene which are characteristic of frostbite in contrast to immersion foot. The reactions to cold injury are described by Kreyberg (93) Apart from the direct injury to cells caused by cooling which may not be irreparable, the subsequent vascular reaction may cause further and fatal injury to cells "It is the fulminating vascular reaction which precedes the tissue necrosis; and the mechanism is probably not through pressure of an edematous fluid, not through thrombosis in its usual form, but rather through the development of stasis"

Similarity of alteration in both cold and heat injury.—Crismon (112) observed that the pathologic and physiologic reactions to cold injury are essentially similar to those seen in tissues reacting to superficial thermal burns Likewise, Rosenfeld and co-workers (113) noted that abnormalities in disordered arterial and lymphatic circulation are strikingly similar in frostbite to those following a hot water burn.

Therapy for frostbite—The effectiveness of heparin reported by Lange & Boyd (114) in preventing gangrene in experimental frostbite has not been confirmed by Crismon or by Quintanilla, Krusen & Essex (115). The results obtained by Schumacher *et al.* (116) were inferior to those prepared by Lange and associates Fuhrman & Crismon (117) further found that not only anticoagulants but vasoconstrictors, steroid hormones, and alterations of blood volume, plasma colloidal osmotic pressure and extracellular phase volume by the use of whole blood transfusion all failed to prevent gangrene following standard cold injury.

Recognition of the similarity of cold to thermal injury led Crismon *et al.* (118) to employ pressure dressings with favorable results in experimental frostbite A more favorable response with rapid rewarming in contrast with moderate cooling was obtained In general, little has been accomplished in the therapy of frostbite to minimize the initial injury or prevent the subsequent gangrene

Immersion foot—Clinically the employment of judicious cooling by

White & Scoville (119) in the treatment of immersion foot reduced or eliminated pain and appeared to be a most effective type of therapy. Although Hemingway (92) concludes that at the present time it remains to be demonstrated by controlled experimentation that cold therapy does more than postpone the ordinary course of events in recovery from cold injury, there appears to be no alternative at the present time but to treat immersion foot in accordance with White's regime.

"Cold" therapy.—The term "physiologic amputation" is employed by Large (120) to denote the use of the tourniquet and refrigeration for the successful removal of gangrenous extremities. Prolonged cooling in tissue not removed can delay wound healing, decrease resistance to bacterial invasion, and may be followed by nerve degeneration Data on reduction in temperature necessary to produce injury are few with respect to normal tissue and are scanty or absent in regard to tolerance by injured tissue. The employment of cooling and cool environments will be discussed further under paragraphs dealing with burns and shock state.

Effects of High Temperatures

In contrast to an extended range of low body temperatures consistent with the maintenance of vital functions, the body's capacity to absorb heat and to function at high temperatures is limited. On the other hand, the process of heat acclimatization is accompanied by characteristic and easily measured physiologic responses in terms of temperature and pulse rate in relation to work and the ability to sweat, and to conserve salt

Tolerance and physiologic effects.—The work of Blockley & Taylor (121) indicates the high environmental temperatures tolerated, e g, 180°F for 49 min. A moderate rise of body temperature, say up to 2 5°F under conditions of work, is not considered harmful and may possibly be considered beneficial A rise of about 10°F. is a representative rectal temperature in the upper range of survival

The stress on the heart is indicated by the increase in rate In data [illegible] of 135 to 140 mark [illegible] upper limit is about [illegible] Further, the difference of 20 beats between reclining and sitting heart rates under heat stress approximates that between reclining and standing rates in debilitated or fatigued subjects These pulse rate alterations would appear to be fundamental in the consideration of heat exhaustion.

Maximal sweat production can approach rates of about 4 l. per hr for short periods according to Robinson (122). In the desert during an eight hour period, some 10 to 12 l of sweat may be secreted, and in industry, some 8 l may be lost during a work shift

Temperature limits with respect to work—In addition to the paper by Yaglou *et al* (96), the report by Caplan (123) on the effects of high environ-

mental temperatures on underground workers in the Kolar gold field is outstanding.

Heat injury.—Caplan (123) described the clinical and pathological manifestations of dehydration, heat stroke, heat cramps, and heat collapse on the basis of his extensive clinical experience. Heat stroke is characterized by restlessness, hot, dry skin, body temperature of 107°F. or higher, full bounding pulse, elevated blood pressure, and high mortality rate occurring within a few hours of the development of symptoms. By contrast, in heat collapse there may be a fall in body temperature, in some cases as much as 3.5°F., with dehydration, hypotension, chloride deficiency, a picture of acute adrenal cortex insufficiency. In heat stroke and more so in heat collapse the water and salt losses are of major importance

Simple dehydration.—During an eight-hour work shift, Caplan (123) considers that a loss of body fluid approaching 5 l is difficult to make up and cannot be replaced during the shift. Efforts to induce individuals to drink quantities of fluid equivalent to the known sweat loss will not be tolerated and if forced will result in vomiting. There may be a large quantity of fluid in the bowel not available to blood tissue. If reserve tissue fluids are low either as a result of defective intake or abnormal loss through secretion, vomiting and vascular clinical signs of dehydration may supervene with *sunken eyes, gross inelasticity of skin, and hemoconcentration,* a condition comparable outwardly to that seen in surgical shock.

Chloride deficiency and heat cramps—Fatigue, asthenia, nausea, vomiting, and cramps may occur if the plasma chlorides fall below 560 mg per l, but this is not invariable In cases of heat collapse, evidence of chloride deficiency can be found in 65 to 90 per cent of cases Caplan (123) and Conn (124) have shown the remarkable adaptation that is possible with reference to salt economy.

Prophylaxis and therapy—Reference is made to the article by Talbott (125) The administration of salt in tablet form has been greatly improved [Consolazio, Pecora & Tusing (126)] by using a slowly dissolving tablet impregnated with cellulose nitrate or acetate forming a multicellular pill. Most of the disagreeable symptoms associated with salt ingestion are eliminated in this manner.

BURNS AND SHOCK

Thermal burns resulting from atomic bomb explosions.—The burn problem in atomic warfare is the subject of a special article by Evans (127) who contributed the chapter on "Shock and Burns" for Volume I of the *Annual Review of Medicine.* The mortality in Hiroshima and Nagasaki from burns of the flash type was 30 per cent in contrast with a mortality of only 10 to 20 per cent attributed to ionizing irradiation. Pigmentations followed a primary erythema associated with the intense infrared and ultraviolet irradiation. The unique and serious problem in connection with atomic thermal burns is the complication of ionizing radiation. Thus, radiation in

significant amount, say 150 to 200 r, will aggravate the symptoms and clinical course of the burn injury. In amounts of 250 r and higher, there would occur not only severe direct local effects but such complications from radiation illness as pancytopenia, loss of resistance to infection, and hemorrhage [Behrens (128)].

Under conditions of a large scale catastrophe, special installations are required for refuge and treatment A practical proposal outlines a plan to install medical aid facilities and supplies in underground garages similar in principle to the Union Square Garage in San Francisco [Behnke (129)] The first aid services of lay personnel will be required and a simple, practical booklet to this end has been prepared for the British Red Cross by Whittingham (130)

To last year's analytical review by Evans are added the following notes which emphasize the importance of temperature, both environmental and local, in the treatment of burns and prevention of shock and of utilizing, especially in the treatment of mass casualties, the plasma substitutes, Dextran and Periston.

Cope (131) summarizes work on burns carried out during and subsequent to World War II. The extensive flash burns at Pearl Harbor posed such problems as whether debridement and cleansing were necessary and the need for surface coagulants The large scale immediate treatment of burns recommended for the military services consisted simply in the application of petrolatum dressings. For individual treatment of burns, real advances were made in promoting convalescence in the removal of necrotic tissue by use of certain chemicals, such as pyruvic acid, and in the employment of skin grafts within 48 hr. after injury.

The difficult problem of therapy appears to be the rapidly changing sequence of pathologic and restorative changes calling for a variety of procedures In the stage of edema, colloid therapy and the restrictive dressing may be called for In the stage of reabsorption of fluid, the presence of colloid may act as retarding agent and excess fluids may bring about pulmonary edema and cardiac decompensation Systematic exploration of these problems in connection with burns has been pursued by Cope and his co-workers.

Rhinelander, Langohr & Cope (132) found, as a result of studies of experimental burns in dogs, that immobilizing restrictive dressings retarded plasma loss, increased lymphatic flow, and displaced edema proximally in the interstitial spaces Offsetting these advantages was the danger from gangrene due to improper application of the dressings.

Again, reference is made to the *Advances in Military Medicine* and the summary reviews on the clinical aspect of shock by Richards (133), experimental traumatic shock by Fine (134), and intermediary metabolism in shock by Long (135). Richards outlines shock research with reference to (*a*) mechanism, (*b*) special inquiries into vasomotor behavior, (*c*) possible chemical or toxic factors, and (*d*) the particular problem of thermal burns. "The most important discovery and one of the greatest practical significance

mental temperatures on underground workers in the Kolar gold field is outstanding.

Heat injury.—Caplan (123) described the clinical and pathological manifestations of dehydration, heat stroke, heat cramps, and heat collapse on the basis of his extensive clinical experience. Heat stroke is characterized by restlessness, hot, dry skin, body temperature of 107°F. or higher, full bounding pulse, elevated blood pressure, and high mortality rate occurring within a few hours of the development of symptoms. By contrast, in heat collapse there may be a fall in body temperature, in some cases as much as 3 5°F., with dehydration, hypotension, chloride deficiency, a picture of acute adrenal cortex insufficiency In heat stroke and more so in heat collapse the water and salt losses are of major importance.

Simple dehydration.—During an eight-hour work shift, Caplan (123) considers that a loss of body fluid approaching 5 l. is difficult to make up and cannot be replaced during the shift. Efforts to induce individuals to drink quantities of fluid equivalent to the known sweat loss will not be tolerated and if forced will result in vomiting. There may be a large quantity of fluid in the bowel not available to blood tissue. If reserve tissue fluids are low either as a result of defective intake or abnormal loss through secretion, vomiting and vascular clinical signs of dehydration may supervene with sunken eyes, gross inelasticity of skin, and hemoconcentration, a condition comparable outwardly to that seen in surgical shock.

Chloride deficiency and heat cramps—Fatigue, asthenia, nausea, vomiting, and cramps may occur if the plasma chlorides fall below 560 mg. per l, but this is not invariable In cases of heat collapse, evidence of chloride deficiency can be found in 65 to 90 per cent of cases Caplan (123) and Conn (124) have shown the remarkable adaptation that is possible with reference to salt economy.

Prophylaxis and therapy.—Reference is made to the article by Talbott (125). The administration of salt in tablet form has been greatly improved [Consolazio, Pecora & Tusing (126)] by using a slowly dissolving tablet impregnated with cellulose nitrate or acetate forming a multicellular pill Most of the disagreeable symptoms associated with salt ingestion are eliminated in this manner

BURNS AND SHOCK

Thermal burns resulting from atomic bomb explosions.—The burn problem in atomic warfare is the subject of a special article by Evans (127) who contributed the chapter on "Shock and Burns" for Volume I of the *Annual Review of Medicine.* The mortality in Hiroshima and Nagasaki from burns of the flash type was 30 per cent in contrast with a mortality of only 10 to 20 per cent attributed to ionizing irradiation. Pigmentations followed a primary erythema associated with the intense infrared and ultraviolet irradiation The unique and serious problem in connection with atomic thermal burns is the complication of ionizing radiation. Thus, radiation in

lytic enzymes. Langohr *et al.* (142) investigated the effect of therapeutic cold on the circulation of blood and lymph in thermal burns utilizing a cold bath (10°C.). Cold reduced lymph flow, edema formation, and rise in protein concentration. These changes were thought to occur as a result of shunting blood flow away from damaged capillaries. There was no alteration in the pattern of arterial blood flow until the extremity was removed from the cold bath when there was an immediate rise The advantages of cold are retardation of development of infection and diminished damage due to impaired circulation, but it was pointed out that cold also reduced the rate of the healing process and that the excessive use of cold may itself cause damage. "More must be known of the critical temperature which can be employed with safety. It seems wise at present to limit the use of cold to temporary alleviation of pain of burns of small extent."

In experimental crush injury to the dog [Fine (134)], gas formation, fever, and early death occurred when the temperature ranged from 24 to 27°C. and at temperatures of 16 to 20°C., gas formation was inhibited Death from muscle injury to one leg was reduced from 100 per cent at 28°C. *to zero at 16°C. Refrigeration of a crushed leg even at room temperature* of 28°C. resulted in survival Refrigeration of the tourniqueted extremity before release of the tourniquet prevented death from shock. All investigators working with shock have stressed the importance of not adding external sources of heat

It is hoped that extensive experiments will be directed to the uniform control of pressure, humidity, and local oxygen supply by such means as plastic envelopes, as well as the maintenance of a determined optimal fluid or gas environment in contact with the burned area.

Plasma substitutes.—In view of the difficulties in the United States during and since World War I attending the development and certainly the large scale production of a satisfactory plasma substitute, it is truly remarkable that there are now available two clinically highly satisfactory substances, Dextran from Sweden and Periston from Germany. Periston, in a 3.5 per cent solution in 500 cc. of physiological saline, appears to be equivalent in its hemodynamic action to 380 cc of a 6 per cent solution of Dextran Selected in 1940 as a plasma substitute by the distinguished pharmacologist Weese (143, 144) of the Bayer Research Laboratories, Elberfeld, Periston is a solution (of the above mentioned concentration) of fractionated polyvinyl pyrrolidone, called kollodon It is a polymerization product developed by Reppe and collaborators in Ludwigshafen am Rhein and originally manufactured as raw material for adhesives, binding materials, etc. Molecular weights of the material used range from 20,000 to 80,000 with a mean of about 50,000 in contrast with the polysaccharide, Dextran, which in the Swedish form contains particles with molecular weights of the order of 100,000 Although chemically inert and similar in action to Dextran there are, on the basis of available but incomplete data, some differences worth

is that in shock following trauma the decrease in blood volume is regularly associated with hemodilution, and the loss from the circulation is that of whole blood and that it occurs at the site of injury."

To the fundamental concept that traumatic shock is largely the result of loss of circulation fluid into injured tissue and the belief held by many that shock and loss of blood are identical [Harkins (136)], are added studies by Rosenthal & Tabor (137), McCarthy & Parkins (138) and Fox & Baer (139) showing the importance of the shift of salts, particularly sodium and potassium, and the need for large quantities of isotonic sodium solutions (third degree burns) to replace the loss of intracellular sodium.

That there are many factors involved in the complicated syndrome of shock is evident from studies in which death could not be attributed to the quantity of fluid lost into the limbs and in which a smaller lethal residual blood volume was associated with hemorrhage compared with trauma. Thus, Fine (134) showed that shock after muscle crush injury appears late (after 24 hr.) and is prevented by chemotherapy. Shock induced by the release of tourniquets appears early and is cured by volume replacement but not by chemotherapy Further, in Fine's ingenious crossed circulation experiments in dogs, a reduced blood flow was associated with hepatic insufficiency and the accumulation of vasodepressor materials in the blood stream.

Of great significance in the elucidation of specific factors causing hemolysis and aiding the development of shock are the studies of Moore & Fox (140). During their investigations of shock in mice produced by tourniquet and by immersion of the hind limbs in hot water, electrophoretic analyses revealed the presence in the blood serum of large quantities of substance having a mobility near that of serum γ-globulin. It was found that the amount of these substances was a function of the environmental temperature of the animals and was also related to the severity of the shock. Thus, at a temperature of 25°C and a humidity of 70 per cent or at a temperature of 35°C. and a humidity of 10 per cent, none of the animals died within 6 hr., but at a temperature of 35°C. and a humidity of 75 per cent or more, the mortality was high, large numbers of mice dying within the first hour after the release of the tourniquets This investigation focuses attention on the importance of temperature, not only of the environment but of injured tissue and the body as a whole

Importance of low environmental temperatures and the localized application of cold.—The employment of low temperatures in the general localized treatment of burns and other types of trauma is of the greatest promise. During the war, the air conditioning of Naval hospital ships [Behnke (141)] was attended by a remarkable improvement and lessened mortality in connection with treatment of burn patients. Conceivably, important factors were decreased loss of fluid by evaporation, a decreased peripheral circulation limiting the absorption of toxic agents, and decreased activity of hemo-

ATOMIC BOMB EXPLOSIONS AND IONIZING RADIATION

It was possible at Bikini to study the biological effects of an atomic bomb explosion on several species of animals and to make follow-up studies, mainly by Cronkite and by Tullis and their co-workers, over a period of several years at the Naval Medical Research Institute and elsewhere. These investigations as well as a comprehensive résumé of the medical aspects of atomic energy are presented in the blook, *Atomic Medicine*, edited by Behrens (157)

Lundie of the Royal Army Medical Corps (158) has prepared a review of the medical aspects of atomic warfare including a list of references that will be most helpful to physicians The blast, thermal, and ionizing radiation effects of the atomic bomb explosions on the Japanese have been reviewed by Howland & Warren (159):

> The chain reaction of atomic explosion produces a spectral range of energies similar to those emanated by a small sun in the absence of a protective atmosphere Ample evidences of radiation were produced, ranging from the extremes of the long heat bands beyond the infrared through the visible spectrum down to the short penetrating wavelengths of the γ-rays

Blast and thermal effects which were responsible for about 80 per cent of the mortality have been mentioned in previous paragraphs

Injury produced by ionizing radiation —Several distinguishing characteristics of irradiation effects are the importance of the secondary rather than primary effects and hence the interval between injury and appearance of symptoms, absence of, or minimal pain, sensitivity of hemopoietic and gonadal tissue, and the lack of specific therapeutic measures The possibility, however, of shielding such sensitive organs as the spleen to effect a great increase in body tolerance is one of the most promising and interesting measures under study by Jacobson & Lorenz (160).

Warren & Bowers (161) have summarized the acute radiation syndrome in man. Hematologic and other effects based in part on the Bikini tests constitute the basis of a series of reports by Cronkite (162, 163, 164) while pathologic aspects of the irradiation injury have been reported by Tullis (165, 166) The book by Bloom (167) on the histopathology of irradiation incorporates much of the investigation in this field conducted in the Argonne Laboratories, University of Chicago, during the war Biochemical effects of irradiation covering work in the Argonne Laboratories and subsequently at the University of Minnesota are summarized by Schwartz (168).

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In other experiments, he has described a recurrent anemia, in effect a pancytopenia, following an apparent recovery six months after the termination of exposure to irradiation. Cumulative effects and permissible dosage limits of ionizing radiation are summarized by Behrens (157)

noting Periston by contrast with Dextran has the property of absorption for dyes and toxins, such as those emanating from diphtheria and tetanus organisms [Schubert (145, 146, 147, 148)]; also, it is taken up readily by the reticuloendothelial system Dextran, on the other hand, may exert a specific diuretic action.

Periston is (a) stable over a wide range of temperatures and apparently can be stored indefinitely, (b) relatively inexpensive and can be manufactured in large quantities, and (c) its use over a period of nine years for the treatment of individual and mass casualties has been attended in its early use by only an occasional reaction attributed to pyrogens In Germany, it has largely replaced plasma and serum as well as analeptics for emergency use. It is, of course, not a blood substitute and is of greatest value administered during or immediately following operations and within the critical period up to about 20 hr. following injury.

In Germany during the war, Periston was given to thousands of patients in the field under conditions of the Russian winter and African summer [Hecht & Weese (149)] Clinical studies have been made by Duettmann (150). In hospitals, patients have received up to 3 l of the colloidal solution over a period of three days. Usually, however, not more than 1 5 to 2 l. are given. Massive infusions in lower animals fill the reticuloendothelial cells with the colloid which may be excreted subsequently without injury [Barfuss & Eichler (151)] In man, accumulation of the colloid in storage cells has not been found [Randerrath (152)]

Many interesting studies with Periston, as with Dextran, are obvious particularly with reference to distribution and possible changes in the colloid as well as possible low grade chronic injury, especially in liver, spleen, and kidney tissue. Finally, it is of interest that one of Germany's outstanding medical contributions has not been studied or utilized more extensively.

A COMMON DENOMINATOR IN REACTION TO INJURY—BLOOD STASIS AND THE CLUMPING OF BLOOD CELLS

Various types of trauma are associated with a slowing and cessation of circulation through injured parts The pioneer work and vivid demonstrations of Knisley and his co-workers (153) of the altered gross consistency of blood in disease and injury invites extensive investigation. The fluorescein technique of Lange & Boyd (154) contributes to an exact description of the histopathologic changes associated with stasis In cold injury, the clumping of cells is not a true agglutination but is described better perhaps by Kreyberg (93) as "conglutination." That erythrocytes are not agglutinated following prolonged stasis was observed by Fulton & Akers (155) in a study of transillumined membranes of the hamster and frog

Begelow, Heimbacker & Harrison (156) investigated intravascular agglutination in the attempt to clarify the meaning of vascular stasis and sludge. Animals exposed to trauma showed agglutinated clumps of red blood cells after injury, which act as emboli in areas remote from trauma.

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Health hazards.—Health hazards in radiation work are outlined by Ingram (169) and by Parker (170).

Basic mechanisms in radiation injury and therapy.—Admittedly, the war studies and those following contained valuable descriptive data but did little to advance the understanding of the basic mechanisms involved in irradiation injury. Barron's investigations, however, have led to trial of the first substances which have had an appreciable protective effect against irradiation. Barron (171) showed that those enzymes which contain sulfhydryl groups are easily inactivated by ionizing radiation and that they may be reactivated by the introduction of reducing agents which contain sulfhydryl groups. The mechanism underlying this reaction has been related to the ionizing effect on water produced by irradiation and the formation of hydrogen peroxide. Patt *et al.* (172) and Chapman and co-workers (173) subsequently demonstrated that cysteine and glutathione exerted a marked protective but not a therapeutic action.

At the sixth international Congress of Radiology held in London, July 23 to 29, 1950 (175), the scope of investigations into the basic nature of radiation injury were revealed by such presentations as the formation of hydrogen peroxide in water exposed to ionizing radiations by Bonet-Maury (of Paris), the elementary process in the radiation chemistry of water and implications for radiobiology by Milton Burton (Notre Dame), the action of x-rays on aqueous solutions including the relationships between radiation effect and chemical structure by W. M. Dale (Manchester, England), a cytological and cytochemical approach to an understanding of radiation damage in dividing cells by A H. Sparrow, L. F. Nevis, & U S. N. Upton (Brookhaven Laboratories), and the bearing of radiation chemistry on the mode of action of radiation by Arne Frossburg (Stockholm, Sweden)

CONCLUDING NOTE

Preventive measures, remarkable often in their simplicity, e.g , the protection against flash burns and crash injury, await application to decrease needless disability and death Against many of the types of injury, therapy is ineffectual or lacks specificity. On the other hand widely different stresses and physical agents induce similar gross physiologic and pathologic alterations. The treatment of the "shock state," whatever the cause, requires preparation and materials that can be provided for well in advance by judicious planning. Meanwhile, the search must continue to find the specific cellular and tissue changes that underlie definitive therapy

The progressive type of investigation as represented by studies of Cope and his co-workers in the field of burn therapy, the fundamental biochemical investigations of Barron, and the systematization by Selye of our knowledge of the acute effects of such stresses as cold, heat and anoxia on the adrenal and other glands and tissues are essential in the attainment of these objectives.

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RADIOLOGY AND RADIOACTIVITY[1]

By L. H. Garland
Stanford University School of Medicine, San Francisco, California

The expanding literature on radiology threatens to engulf the serious worker. Since radiology embraces the diagnostic and therapeutic applications of radiant energy in the entire field of medicine, this expansion is both understandable and inevitable. Add to this the explosive field of radioactivity in medicine and you reverse the comment of Louis XIV on the deluge If, therefore, some significant contributions are omitted from the following paragraphs, it is not necessarily because of lack of space; they just have escaped the attention of your reviewer!

Contributions will be considered under the two main headings of diagnosis and therapy, with subdivisions of each on an anatomical site basis Only brief reference will be made to some of the experimental radiological work currently in progress, biological, chemical, and otherwise Those interested must refer to the various Cumulative Indexes, notably those of the journals *Radiology* and *The American Journal of Roentgenology* These, together with the *Acta Radiologica* and the *British Journal of Radiology*, cover most current clinical investigative work in this field For therapeutic data, the annual reports on patients treated at the Radiumhemmet (all cases since 1921, kept up to date annually) available from Stockholm and the quinquennial statistical reports from the Holt Radiation Institute, Manchester, are invaluable

RADIOLOGY IN DIAGNOSIS

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These articles are of fundamental importance and are on a par with two papers dealing with the physical factors which influence the quality of radiographic images. The first of these is a monograph by Nelson (73) and the second a paper by Newell (74) on "Threshold Visibility of Pulmonary Shadows."

Newell noted that on a smooth background, a 1 mm. cylinder of soft tissue density casts a shadow which is just perceptible. For sharp shadows 6 to 60 mm. sq , the visibility is independent of the size. Through the lungs, the threshold is 6 per cent absorption and is nearly independent of voltage; however, at voltages above 100 kv. with a 3 mm. aluminum filter, visibility is *slightly increased. A shadow which is not sharp is significantly less visible* (12 per cent central absorption in comparison with sharp ones at 6 per cent)

The great need for improved standards of technique and interpretation is illustrated in a study by Garland (34) on the reliability of mass chest x-ray surveys. Working with a group of collaborators, it is shown that the reader error is of significant degree in such surveys and tends to vitiate their value (minimal error 30 per cent under-reading and 1 per cent over-reading). To reduce this error, we must use tested readers, dual readings, and minifilms of the highest technical quality.

The differential diagnosis of solitary pulmonary lesions was reviewed by Arbuckle (4) in sound clinical fashion. He concluded correctly that biopsy must often be resorted to. The diagnosis of pulmonary arteriovenous fistula was summarized by Duisenberg & Arismendi (24) and also by Yater *et al* (103) with good reviews of the literature on this curable lesion. The problem of alveolar cell carcinoma of the lungs was extensively discussed by Good *et al.* (40). Lampe & Zatkin (59) reported a group of five cases of pulmonary metastasis from mucous and salivary gland tumors (pseudoadenomatous basal cell carcinomas), all five being of a very slow growing type, many without pulmonary symptoms for as long as five years Robbins (84) regards cholesterol pneumonitis as an important entity, Hampton, in discussion [see (84)], wondered if the lamp used to illuminate his microscopic sections might not need replacement!

Furcolow (33) reported further investigations on pulmonary calcifications developing in persons with sensitivity to histoplasmin, plus further bacteriological and clinical observations on histoplasmosis. His papers are well illustrated. Di Rienzo (23) reported results of observations on the physiology of the bronchial tree in roentgen studies with various contrast media, using fluoroscopy, spot films, and conventional roentgenography. *He believes that* he had demonstrated true bronchial peristalsis, the existence of functional bronchial sphincters, etc. If confirmed, this contribution will be a significant one in explaining some of the phenomena of cough, of bronchiectasis, and so forth.

Cardiovascular System

Methods for refining or improving the diagnosis of congenital cardiovascular lesions multiply with the current improvements being obtained from surgical procedures on congenital heart cases. Unquestionably, the most

brilliant work of the last 12 months is that reported by Wegelius, Lind, and co-workers (31, 63). Wegelius is a Finnish radiologist practicing in Stockholm and Lind is a Swedish pediatrician and cardiologist. Working together, they have evolved an apparatus for direct serial roentgenology of the thorax in two planes simultaneously, making as many as 12 films per sec. in each plane for a period of perhaps 4 sec. They, therefore, end up with about 100 views, half of them at right angles to each other; the intervals are 0 08 sec., and the exposure times as short as 0 02 sec. Your reviewer has observed this apparatus in action in Stockholm and seen the results obtainable with it. The roentgenograms on small children are certainly beautiful and illustrate physiological facts previously not known (such as "systole" of the superior vena cava simultaneous with right auricular systole, contractions of the pulmonary artery segment following right ventricular systole, etc). The infant or child lies on a bakelite insulated "L" which permits simultaneous electrocardiograms during the roentgen exposures The cassettes are of a special cardboard type and are whirled through the apparatus into two collecting sacks Wegelius regards his unit as merely a preliminary or rough model and, with the aid of his engineer (Fredzell), will doubtless evolve even more efficient types

Lind (62) published an excellent monograph on heart volumes in normal infants, an exhaustive treatise on this subject An able and sensible symposium on the diagnosis of congenital cardiovascular diseases by simple clinical and radiographic methods was published by three groups of authors during the year Shapiro (89), who dealt largely with the clinical aspects, Peck & Wilson (78) with conventional radiological procedures, and Stauffer (96) with radiological procedures in operable lesions

Progress in opacification of the cardiovascular system proceeds daily. Jonsson (55) reported some neat results in the diagnosis of difficult cardiovascular lesions by means of selective angiocardiography (injecting the opaque medium via catheter) Others, notably notably Weyde (100), reported results of aortography with pressure devices. Weyde has done over 100 abdominal aortograms by inserting a long needle below the left twelfth rib, directing cephalad and mesiad into the upper abdominal aorta He uses a very simple pressure machine to inject the 70 per cent iodopyracet (Diodrast) rapidly. Three films are made in most cases, one to show the arterial tree, one the venous, and, finally, one the presence of any residual pooling in lesions such as hemangiomas, etc The method is of distinct value in the differential diagnosis of some abdominal arterial occlusive lesions, some renal disorders, and some intra-abdominal tumors.

Phlebograms continue to be used in the diagnosis of patency of the deep venous circulation of the legs as a preliminary to surgical treatment of varicosities and in the diagnosis of various obscure masses involving the lower extremities The current trend is to perform erect phlebograms; the patient lies almost vertically on a tilt table and about 80 cc of 35 per cent iodopyracet or similar material is injected into a small vein near the big toe (51). This mass of opaque medium moves sufficiently slowly to permit leisurely

study of the venous circulation, especially when suitable tourniquets are applied above the ankle and below the groin (in order to direct the opaque medium into the deeper veins).

Gastrointestinal System

The problem of the prevention or early detection of gastrointestinal tract carcinoma continues to engage the activities of many scientists. There has been little significant progress in the matter of earlier diagnosis of curable gastric cancer. The incidence of gastric cancer in the United States is estimated at about 22 cases per 100,000 population (all ages and sexes) This figure increases to about 45 per 100,000 adult males. The potential yield by survey methods is obviously uneconomic and impractical, Hilleboe (48) to the contrary notwithstanding!

The earlier detection and removal of colon polyps will decrease the problem of colon cancer. Gianturco (37), both in a discussion and in a separate paper, emphasized his preference, based on some 14 years' experience, for single contrast enemas made with heavy exposure. He regards this as superior to double contrast studies. On the other hand, Moreton *et al.* (71) believe that properly performed double contrast studies are essential Both agree that the problem of fictitious polyps is still a considerable one. Hawley (46) illustrated another misleading appearance due to ileal prolapse, which is not infrequently reported as cecal polypoid tumor. We believe that single contrast, heavy exposure studies are not sufficiently used and would yield correct diagnoses in a high percentage of patients currently subjected to the hazard and inconvenience of double contrast studies

Frank & Paul (30) reported an unusual case of congenital reduplication of the esophagus in a 10-year old boy. Zatkin & Riera (105) reported on the roentgenographic appearances of the upper gastrointestinal tract in a series of patients following various surgical procedures. The difficulty of interpreting roentgen findings following juxtagastric operations is sufficiently great to warrant further study of this problem.

Pylorospasm is said to be relieved by oral procaine (50 to 100 cc. of a 1 per cent solution, taken twice daily for several days). Roka & Lajtha (85) claim no reactions, but the reviewer hopes they have some oxygen handy.

Genitourinary Tract

Newer drugs for demonstration of the urinary tract by intravenous administration continue to be sought. One of these, sodium acetrisoate (Urokon Sodium), was extensively tried during the last year and appears to be as satisfactory as its predecessors with even fewer side effects Your reviewer was interested to observe the widespread use of compression in connection with intravenous urography in the Scandinavian countries at the present time. A compression belt consisting essentially of a flat lucite plate, held in place with two small canvas straps, is placed over the lower abdomen Im-

mediately following intravenous injection of the opaque medium, a small rubber bulb the size of a tennis ball is inflated between the lucite portion of the "belly band" and the patient's lumbosacral angle. This bulb is inflated just as one would inflate a blood pressure cuff, the degree being gauged to the patient's comfort. The compression is left on the patient 10 min , then the first film is made. After suitable roentgenograms of the renal pelvis, calices, and upper ureters have been obtained, compression is released and the lower ureters studied. Your reviewer is convinced that for most clinical work, adequate compression is as essential as adequate dehydration in securing intravenous urograms of the highest technical quality (57).

For urethro-cystographic studies, the trend is to use viscous opaque media injected with gentle pressure under remote control, films being made during injection, after injection, and during micturition. These films give valuable information concerning the physiological and anatomical status of the bladder, prostate, and urethra [Edling *et al.* (25)].

Central Nervous System

The subjects of displaced physiologic intracranial calcifications, erosions of the sella turcica, and meningiomas were thoroughly reviewed during the year in a symposium which included papers by Young (104), Camp (13), and Pendergrass (79) Of particular note is a paper on eighth nerve tumors by Hodes & Pendergrass (49); this is a model paper on the roentgen diagnosis and differential diagnosis of this important and curable type of tumor.

The status of myelography, past and present, was reviewed in the annual Carman Lecture by Camp (14). He points out that the ideal opaque medium has not yet been found; ethyl iodophenylundecylate (Pantopaque), in oil, is probably the best generally available medium today Scandinavian workers are rather fond of watery opaque media, but these have the disadvantage of requiring preliminary spinal anesthesia, maintenance of the patient with the head and thorax relatively high during and for some hours after the examination, plus a small risk of undue meningeal irritation. Lindblom (64), working at the Karolinska Hospital in Stockholm, has performed direct injection of one or more lumbar intervertebral discs in about 60 cases. Using from 1 to 3 cc of an opaque solution such as iodopyracet, he has been able to show the actual point of rupture and the distribution of the opaque medium in the extruded nucleus pulposus or disc The value of this method remains to be seen, but it is the first time that the actual rupture has been demonstrated by direct methods in living human beings.

Cerebral arteriographic procedures continue to be explored quite vigorously Wise *et al* (101) review the subject and add some cases of their own. Lindgren (65) has succeeded in performing percutaneous angiography of the vertebral artery in several cases. Your reviewer has watched radiologists insert a long needle through the skin in the supraclavicular fossa and reach this vessel successfully, the entire procedure being done under local anesthesia with a happy combination of anatomical skill plus celestial luck.

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isotopes is emphasized by Failla (26). He thinks that each worker should acknowledge the permissible limits of exposure and strive to keep his own exposure well below such. These limits, for whole body exposure to x- or γ-rays up to 3 million volts, are 0.3 r per week measured in air; for local exposure limited to the hands, 1.5 r per week or, in the case of β-rays, 1.5 r per week, measured at the basal layer of the epidermis. Brues (11) points out that the effects of large dosages of radioactive isotopes resemble those of total body irradiation, allowing for tissue distribution.

The hazards of the ubiquitous shoe-fitting fluoroscope are wisely stressed by Lewis & Caplan (61); it is impossible to justify the continued use of this potentially hazardous weapon for such futile purposes. Shoe-fitting fluoroscopes should be abolished from stores and departments, especially those to which children have access.

Degoy & di Rienzo (22) published a small monograph on artificial anterior pneumomediastinum in infants, in connection with the early diagnosis of thymic hyperplasia The illustrations are of considerable interest and help to clear up many problems related to upper mediastinal shadows.

Technical Developments

Besides the remarkable high-speed serial radiographic device developed by Wegelius and his associates mentioned above under Cardiovascular Systems, two other devices merit commendation and study. One is the rapid automatic serialograph for roll films (10 in wide) developed by Scott & Moore (88) which is extremely useful for high-speed study of the cardiovascular apparatus in adults, of the cerebral circulation, and of other portions of the body. The other is a somewhat similar, but even more rapid roll-film device, developed by Hodges of Ann Arbor This also permits from two to four films per second of the adult heart Hodges and his associates (50) at the University of Chicago continue their work on improved x-ray phototimers

There has been further interest in horizontal body section radiography during the last year. Stevenson (97), of the Royal Free Cancer Hospital in London, has perhaps the most experience and the most balance in this matter; the apparatus was of singular value in a case of double aortic arch, but not of outstanding value in other pulmonary problems Nevertheless, it is a new tool of possible anatomic and clinical use Gebauer (36) goes into the problem of horizontal body section radiographic work fairly exhaustively

Bell (8a) of Brooklyn and Watson (99a) of London have done further work on multiple simultaneous horizontal tomograms In the Scandinavian countries, one sees a considerable amount of vertical tomography, and the Belgians have developed a very neat apparatus for making rapid serial tomographic films in the erect position which has promise of being very useful in some questionable cavernous lesions in dense portions of the lungs.

Improved scatter-reducing cross-grids are being developed and are essential for simultaneous right angle radiography. A Finn named Paatero (76)

Osseous System

Methods for improving the diagnosis of joint disorders, such as double contrast arthrography, continue to be developed. While of great anatomical interest, the real clinical value of these methods remains to be established

Holt & Owens (52) report the bone changes of sarcoidosis in a series of 65 cases. They concluded that only 15 per cent of their cases show definite roentgenographic bone changes. However, they did not stress sufficiently the element of time in the detection of these lesions Sarcoidosis is a systemic disease of great chronicity in some cases. Bone lesions may be visible one year and not another. We believe that, under serial observation, they are demonstrable in about 25 per cent of cases. Carroll & Evans (17) discuss the bone changes in sickle cell anemia and report additional findings, of importance especially in the southern parts of this country.

Inasmuch as the roentgen findings of greatest interest in Cushing's disease (pituitary basophilism) are the bony ones, it would seem appropriate to draw attention here to the excellent paper by Sosman (94) on this subject With the production of Cushing's syndrome by protracted adrenocorticotropic hormone (ACTH) and cortisone administration, this paper, with detailed reports on seven idiopathic cases, is most timely.

Miscellaneous Investigations

The use of radioactive isotopes in clinical investigation continues to arouse considerable interest An excellent summary of the present knowledge of this subdivision of radiology, published in book form by Low-Beer (67), augments the fine outline on radioisotopes in clinical diagnosis prepared by Newell (74a) for Volume I of this review Like Newell, he stresses the point that clinical measurements and isotope dose determinations are not yet very accurate procedures You may remember Newell's note on the samples of iodine 131 which were sent to institutions actually known to be working with this particular isotope; their measurements of the standard varied from one-half to twice the average value, an error of no mean dimensions Miller [in (67)], who did extensive work with Low-Beer in radioiodine determinations, also stresses the difficulty of isotope measurement in even the most practiced hands

The influence of radioisotopes on biochemical thought and practice is discussed by London (66) as part of an extensive symposium on radioactive isotopes. He regards two principal developments as being the result of tracer techniques, namely greater appreciation of the dynamic state of the body constituents and greater insight into the mechanism of biological synthesis Marshak (68) reports further work on the use of radioactive phosphorus in the study of the metabolism of normal and neoplastic tissues. The following subjects are particularly considered: phosphate esters and carbohydrate metabolism, nucleic acids and nucleoproteins, x-ray effect on nucleic acid turnover, and deposition in bone

The problems of protecting personnel employed in the use of radioactive

of the eyes. We know no radiologists who would attempt to pursue or prescribe surgical procedures on the eyes, but there are apparently some ophthalmologists who prescribe roentgen ones. The doses reported make your reviewer shudder. For example, Guyton & Reese (42) report a series of 12 cases of retinitis proliferans treated with doses of from 3,500 to 15,000 r. They report giving from 1,000 r to 10,000 r, measured in air, to fields 2.5 cm. in diameter on the temporal and nasal sides of the affected eye. If these patients survive long enough, the condition of the irradiated skin, soft tissues, and bone is not going to be very healthy.

The judicious use of modest doses of roentgen irradiation for benign occular disorders is well established; we believe it is of great value in certain cases of hypervascular corneal scars, certain types of iritis, inflammatory lesions of the lids, etc. However, dosages should rarely be in the four figure level.

Radiotherapy for hyperthyroidism continues to arouse considerable discussion. Internal radiation by radioactive iodine has caught the attention of many workers, despite the fact that doses are more difficult to calculate and control than external irradiation with conventional roentgen therapy beams. We wonder if radioactive iodine would not be more useful as a diagnostic (tracer dose) weapon to control the efficacy of roentgen therapy in hyperthyroidism than as a primary therapeutic weapon Crile & Rumsey (20) report a series of 38 cases of subacute thyroiditis in which they obtained "prompt and complete results" with doses of from 600 to 800 r, measured in air.

Of the many forms of human rheumatism, ankylosing spondylitis in young adults is one of the most crippling. Roentgen therapy in moderate dosage is valuable in relieving the pain and disability of this condition. Spishakoff & Low-Beer (95) report a series of 125 cases of ankylosing spondylitis treated with roentgen therapy. They believe that the results were proportionate to the dosage. of 11 patients who received one course of treatment, about 50 per cent obtained long-standing relief; of 73 cases who received three courses, 86 per cent obtained such relief. The courses consisted of 600 r in air to each of three or four fields over the spine posteriorly This total dose of 600 r is repeated in one month and again after three months. Such therapy is now of well established repute and of great value in perhaps 75 per cent of cases.

The results of roentgen therapy of the adrenal glands in the cases of angina pectoris aroused some interest several years ago. Raab (83) brings us up to date on his own series of 200 cases in a recent article Unfortunately, no controls are reported, and we fear his conclusions are over optimistic

Neoplastic Diseases

The field of radiation therapy in neoplastic diseases is an ever-expanding one. It has been estimated by Garland (35) and others that about 60 per cent of all cases of neoplastic disease require irradiation either for cure or palliation at some time in their course. The great need for standard methods of

has developed an intriguing technique for the radiography of curved outer surfaces; the resulting films of the mandible and skull are quite startling.

Adolph (1), Kaplan (56), and others continue to work on *improved* barium preparations for roentgen diagnostic purposes. In Kaplan's hands, a special colloidal barium sulfate suspension has proved of great value in some gastrointestinal problems. The long awaited electron-fluoroscope is still on the drawing boards, but, like the man in the moon, is indubitably there.

RADIOLOGY IN THERAPEUSIS

Infectious Disorders

Despite the availability of new and improved antibiotics, better endocrine preparations, and general hygienic advances, cases of severe acne vulgaris still trouble the practicing physician. Quastler (80) reported the results of different roentgen therapy techniques in a group of cases. While his conclusions are rather sweeping in view of the small number of cases in each of the groups treated, your reviewer believes that his work is important and sustains the value of wisely given roentgen therapy for this ailment. One presumes that ordinary measures have always been exhausted before resorting to so powerful a weapon as roentgen irradiation, and that this weapon is employed only by a well trained individual

Another severe chronic inflammatory disorder of the skin and its appendages which sometimes defies medical and surgical procedures is hydradenitis suppurativa axillaris. Schenck (86) reports results in 54 cases with this stubborn condition and illustrates the value of radiation therapy.

Hultberg (53) treated an interesting group of cases of tonsillar infection with short distance, low voltage roentgen therapy. Now that the tonsil is ceasing to be an organ automatically removed from our younger citizens, the possibility of having to handle infections by nonsurgical means rearises Hultberg is an experienced radiation therapist, and his results are believed to be reliable.

Lampe *et al.* (60) report the result of "concentrated roentgen therapy" in cervical tuberculous lymphadenitis. This condition is still not uncommon and may prove very stubborn. Streptomycin therapy requires several months and has side effects of potential neurological hazard (21); Lampe, by giving a course of four or five treatments in one week, was able to control most of a small series of 37 cases. His doses are within the reasonable range, and his technique quite interesting in view of the fact that most radiotherapists tend to treat these cases by small weekly doses spread over 12 weeks. The convenience and economy of four or five days' treatment is obvious.

Miscellaneous Nonneoplastic Disorders

The use of β-rays in various ophthalmologic conditions continues to be expounded, chiefly by those who do not realize that low-voltage roentgen rays have a similar biological action, are more easily controlled, and are more accurately measured The new β-ray emitters produced as a result of the atomic pile will probably increase the number of needless radiation injuries

hemmet between 1936 and 1941. The author believes that radiation therapy does not enhance the results of Stage I cases, but observes that it is not always possible clinically to determine that the lesion is Stage I preoperatively. He believes that a combination of radiation and operation is advisable in Stage II and that radiation alone is the superior weapon in most cases of Stage III breast cancer We heartily concur.

A comprehensive symposium on cancer of the *cervix uteri*, in which seven authors take part, is presented under the direction of Arneson (5). The majority of workers in this field now recommend a combination of external roentgen therapy plus carefully applied intracavity radium for the cure of this common malignancy The technique of external roentgen therapy varies in different clinics, the doses reaching what your reviewer regards as potentially hazardous levels in some hands, notably the doses of Fletcher (29).

In Volume 5 of the *Annual Report on Radiotherapy in Cancer of the Cervix*, Heyman *et al.* (47) compile the results on 7,675 cases from 10 selected centers which have been reporting five-year results for over a decade. For the period 1936 to 1941, these centers obtained a relative five-year cure rate of 38 per cent This compilation is a model of "site" cancer statistics and a tribute to the untiring work of Professor Heyman

Tumors of inaccessible sites —Cancer of the *larynx* continues to be treated by radiotherapy or surgery, depending on the experience and enthusiasm of the attending clinician. The cure of early cases of laryngeal cancer is not difficult by either method (80 per cent five-year arrests); radiotherapy leaves the patient with a good voice. Far advanced case cure by any method is difficult, perhaps very radical surgery offers more than radiotherapy for attempted cure, but not for palliation [Jackson (54), Harris (44), Cutler (19)]

Cancer of the *bronchus* remains a baffling lesion. Squamous cell tumors are difficult to cure by any method; surgery offers more hope than radiology Some of the other malignant pulmonary tumors, if still lobar in localization, are amenable to excision Postoperative irradiation of the affected hilum or reliance on radiation alone is not uncommon in British clinics, but the cure rate is very low.

Cancer of the *esophagus* rarely manifests itself early and is usually incurable by any known means In order to make patients with obstructive symptoms more comfortable, radiation therapy is commonly employed, either multiple fields or rotation technique Krebs *et al.* (58) report the results by a fairly large group treated by rotation roentgen therapy with figures similar to those obtained in Copenhagen (not more than 3 per cent of five-year arrests) The method is very time-consuming, and its superiority to simpler techniques or to palliative surgery is to be doubted

Harvey (45) presents a comprehensive paper on the results of roentgen therapy in *Wilms tumor*, together with an extensive bibliography He regards roentgen therapy as a useful postoperative measure in most cases. Wittenborg (102) reports the end results of roentgen therapy of malignant

reporting in order to permit evaluation of results is nowhere more manifest than in the field of neoplastic diseases For almost 25 years, the Swedish school has been stressing the importance of absolute figures, that is, results based on all cases seen, not merely on those treated. Only a minority of surgeons and radiologists so report. Most workers report relative figures, that is, results based only on cases treated by surgery or radiation.

For purposes of brevity, we shall consider this subject under the headings: *(a) Tumors of accessible sites, (b) Tumors of inaccessible sites,* and *(c)* Lymphoblastoma and leukemia.

Tumors of accessible sites.—The results of radiological and/or surgical procedures in the control of cancers of the *skin, lip,* and *oral cavity* were summarized in a symposium (15) published by the American College of Surgeons in 1950 The curability of skin cancer is reported in the range of 75 to 85 per cent, of lip cancer 56 to 88 per cent, and of tongue cancer 14 to 50 per cent. Since few workers exceed cures of 20 per cent in tongue cancer, this 50 per cent figure for the tongue must refer only to small or early lesions of the anterior half, and not to all tongue cancer.

A comprehensive series of reports on radiation therapy *of cancer of the tongue* by authorities such as Baud, Berven, Windeyer, and Wood was published in the *American Journal of Roentgenology* for 1950 (8). This can be heartily recommended to all interested in this serious form of cancer

The present place of roentgen therapy in operable and inoperable cancer of the *breast* is reported in the *American Journal of Roentgenology,* Volume 62. The authors include Berven (10), Haagensen (43), McWhirter (70), Taylor (98), and Baclesse (7). McWhirter presents the most convincing data. This radiologist, working at the Royal Infirmary in Edinburgh, has treated several hundred cases of cancer of the breast in conjunction with surgeons from all over Scotland. The basic method of attack is simple mastectomy followed by early postoperative roentgen therapy, about 15 treatments being spaced over a period of 2 5 weeks and arranged so as to deliver a dose of approximately 3,700 r into the tissues of the axilla, supraclavicular fossa, and chest wall. The figures of McWhirter are the best absolute figures published for such a large group of cases: 41 per cent five-year survivals. However, before one can unreservedly recommend his method, one must await its confirmation at the hands of other workers

Guttman (41) reports a series of 82 cases of primary inoperable cancer of the breast treated by roentgen therapy alone with modest results. Baclesse (7) believes that he can obtain superior results by extremely protracted roentgen therapy, delivering doses equivalent to about 200 r twice a week to each of several fields about the breast and regional node areas for a period of four months. Of 131 inoperable cases treated over five years ago, 41 are reportedly alive and clinically well.

The most thoroughly documented monograph on cancer of the breast which has appeared in recent years was published in the end of 1949 by Nohrmann (75). This is a clinical study of 1,042 cases treated at the Radium-

greater extent than the tumor because of the "Compton effect of the recoil electrons " However, if it becomes possible to limit the effects of radiation selectively to the tumor cells by added chemical or other means, the higher potentials may bring improved results.

An apparently economical form of supervoltage apparatus is the projected radioactive cobalt bomb or cannon Myers (72) reports on observations with radioactive cobalt in simple applicator form. The γ-rays of radioactive cobalt are similar in action to those of radium, and therefore, improvement in clinical results merely because of the isotope is improbable. Quimby & Braestrup (81) offer constructive suggestions for the planning of a radioactive isotope program in an average institution, and an editorial in a subsequent issue of the same journal deals with the problem of disposal of radioactive wastes in a general hospital.

Radiation Physics

The depth doses of electrons obtainable from the betatron are described by Skaggs (92). It is hoped that this weapon will have some use in certain *deep-seated tumors, but clinical data are still lacking The physics of most* presently known types of radiations are discussed in the encyclopedic second volume of *Medical Physics* edited by Glasser (38). Sievert (91) and his coworkers take an entire issue of *Acta Radiologica* to report on medical radiophysics in Sweden from 1920 to 1950. This is highly recommended reading Parker (77) gives us his ideas on dose units for mixed radiations. This important problem is not yet solved.

Radiobiology

Andersen (3) discusses the problem of differentiation following irradiation. He made observations on some 660 malignant tumors in animals and human beings but failed to produce the apparent increased differentiation reported by Glucksmann (38a) of the Strangways Research Laboratory at Cambridge In Andersen's opinion, all of the changes in irradiated tumors represent nonspecific cellular degeneration

Snyder & Kisieliski (93) discuss the relative biological effectiveness of roentgen rays and β-rays; in the particular material which they investigated, the relative effectiveness appeared to be in the order of 1.4 to 1. Presently available data on the radiobiology of radioactive isotopes is ably presented by Low-Beer (67) in his monograph

An interesting unit of radiation dosage is proposed by Cohen (18), termed the rec or roentgen equivalent clinical. He describes the relative biological effects of specific ion density, overall time, and field size so that equivalent dosage can be obtained under any treatment condition. One kilorec is equivalent to one standard erythema dose under all treatment conditions. He has constructed nomograms enabling the tumor dose "which is most likely to be effective in a given set of circumstances" to be computed He believes that when relatively short-lived radioactive sources are used in

neuroblastoma (adrenal and abdominal) in 73 cases seen at the Children's Hospital in Boston. The results are fairly good: 30 per cent absolute three-year survivals; 60 per cent relative three-year survivals in cases without metastases (surgery alone in small lesions, surgery and spotoperative irradiation in more extensive ones).

Bachman & Harris (6) report the results of radiation therapy of 64 cases of *pituitary adenoma*. They record an apparent correlation of tumor dose with favorable response in these cases.

Taylor (99) and Martin (69), in surgical and radiological papers, discuss the best method of handling metastatic carcinoma in *cervical lymph nodes* These important papers are recommended to students of this problem.

Lymphoblastoma and leukemia.—The results of radiation therapy in the pulmonary manifestations of Hodgkin's disease are analyzed by Sheinmel (90) on the basis of a fairly extensive experience He compares the apparent results from roentgen therapy alone and nitrogen mustard therapy alone and is of the opinion that the former is less toxic and preferable as a primary weapon. Mustard is valuable in advanced and apparently radioresistant cases.

Friedell & Storaasli (32) discuss the selective take-up of radioactive phosphorus by various normal and tumor tissues. They regard primary polycythemia and chronic myeloid leukemia as suitable for such treatment, reporting 10 cases of the former and 15 of the latter However, no data are presented to show that the results are superior to those obtainable by judiciously applied external roentgen irradiation, either total body or local

Miscellaneous, Including Technique, Equipment, Etc.

The relative merits of "standard voltage" and "supervoltage" equipment continue to be a subject of debate. Some 15 years ago, there was considerable hope in the United States that supervoltage roentgen therapy might result in superior clinical results; sufficient time has now elapsed to know that, unfortunately, this is not the case Schulz (87), on the basis of considerable experience with intraoral and throat carcinomas, noted no significant improvement with million-volt over conventional therapy. Cantril & Buschke (12, 16) believe that it has some merits, but that their own results "are not statistically superior to those achieved at the Institut du Radium using a comparable technique and 200 kilovolt x-rays " Robinson, who executed considerable careful work with Stone in the early 1940's, reminds us that their patients were just as nauseated and had just as much diarrhea with supervoltage as they did with orthovoltage. This, of course, is to be expected.

Roentgen therapy at 200 kilovolt potential (KVP), with 1 or 2 mm of copper filter, remains the most valuable weapon of the radiation therapist. In lesions at any depth, it permits a reasonably good tumor dose without skin damage. Belot (9) regards the higher potentials (even in the multimillion volt range) as being as apt to damage the deeper normal structures to a

Fig 2. Flash effect of a hydrogen bomb 1,000 times more powerful than present bombs would be relatively greater than its blast effect. The Hiroshima bomb caused fatal burns at distances up to 4,000 to 5,000 ft (small circle) A hydrogen bomb would cause fatal burns at distances of 20 mi or more (large circle) The inhabitants of Chicago and its suburbs could thus be wiped out [This information was compiled by the editors of *Scientific American* (82b) on the basis of previously published material]

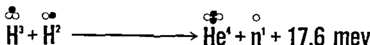


Fig 3. A tritium and deuterium reaction would release more energy than any other reaction involving these heavy isotopes of hydrogen Tritium is H^3, or the hydrogen isotope of mass 3 Its nucleus is composed of one proton (small white circle) and two neutrons (small black circles). Deuterium is H^2, or the hydrogen isotope of mass 2 Its nucleus is composed of one proton and one neutron When these two nuclei are brought together, they form helium of mass 4 (He^4), a neutron (n^1) and 17 6 million electron volts of energy (mev) Unlike the reaction of a neutron and a plutonium nucleus, this reaction does not yield products that can perpetuate it (82a)

therapy, there is a critical interval of time during which the biological efficacy is approaching a maximum. Clinical dosage prescriptions must be calculated for this critical interval, and doses based on shorter or longer time intervals are likely to prove excessive. He offers a formula whereby critical biological intervals can be determined for isotopes having various half lives. This series of papers is an ambitious attempt at reducing biological variables to their lowest common denominator.



FIG. 1 Blast effect of present and proposed atomic weapons is projected on a map of New York City and the surrounding area. A uranium bomb set off above midtown New York would cause severe destruction within a radius of 1 mi. (small circle), a hydrogen bomb 1,000 times more powerful would cause severe destruction within 10 mi. (large circle). (This information was compiled by the editors of *Scientific American* (82b) on the basis of previously published material.)

The literature on atomic energy continues to effloresce. Under the direction of the Los Alamos Scientific Laboratory, the United States Department of Defense and the Atomic Energy Commission have published a treatise on *The Effects of Atomic Weapons* which has almost reached the best seller lists. While intended primarily for those concerned with the planning of civilian

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defense, this treatise is virtually a source book on nuclear radiations, their generation, measurement, effects, and allied matters. Glasstone (39) and his associate editors are to be congratulated on this comprehensive work.

The development and implications of the hydrogen bomb are expounded in a series of articles appearing in the *Scientific American*. Ridenour (82a) presents an account of the theoretical background of the weapon and a discussion of some questions in regard to our present policy of security. Bethe (82b) illustrates the nuclear reactions involved, the time required for their development, and illustrates the tremendous flash hazards of this weapon (fatal burns at distances of 20 miles or more). Bacher (82c) follows these two distinguished physicists with a discussion of the strategic and moral aspects of the weapon and, finally, Lapp (82d) illustrates the appalling problem of organizing an effective civilian defense against the hydrogen bomb. These four articles are well illustrated and thoroughly discouraging.

Allen (2) and his associates discuss the treatment of irradiation sickness based on a six-year study of the effects of irradiation conducted at the University of Chicago. This authoritative article is part of a group of 15 dealing with defense against atomic attack published in a special issue of *The Bulletin of the Atomic Scientists*. This issue contains some of the most frank discussions of the entire problem which have appeared to date in the American literature. The article on irradiation sickness is important in illustrating how little can be done for casualties of this type.

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LABORATORY AIDS TO DIAGNOSIS AND THERAPY[1]

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It is obviously impossible in the short space allotted to cover exhaustively the subject which has been assigned to this author. A review that attempted this could be no more than an uncritical "catalog of the ships," a proper assignment for a bibliographer. Instead, the author has confined his attention to a few topics that appear to him to have peculiar significance and with which he has had sufficient experience to lend to his opinions some semblance of expertness and authority. In consequence of this policy, undue weight may seem to be given to studies with which he has been connected.

Iodine and Thyroid Disorders

Protein-bound or precipitable iodine of serum (SPI).—The presence of iodine in the thyroid hormone and the segregation of this element in the thyroid gland early raised hopes that it might be possible to devise methods for the direct measurement of thyroxine in the blood by chemical procedures. Although simple measurements of total iodine provided information of some value, the inclusion of inorganic iodine was a confusing feature, limiting the diagnostic and therapeutic value of these measurements and rendering them almost entirely useless when persons were receiving iodine compounds for therapeutic purposes Early efforts to differentiate organic or hormonal iodine by ethanol extraction were not altogether successful It was demonstrated, however, that most of the iodine in blood is confined to the plasma and is nondiffusible (1), while inorganic iodine, added either *in vitro* or *in vivo*, enters blood cells (1, 2) and can be removed from serum by dialysis (1). It was further discovered that the iodine in serum can be precipitated with the proteins to which it is so firmly attached that it is not removed from the precipitate by repeated washing that will remove all inorganic iodine (1 to 6) Thyroxine added to blood *in vitro* behaves in this respect like the intrinsic protein-bound iodine (1, 3, 5) Some diiodotyrosine also seems to adhere to the proteins (1, 5) Taurog & Chaikoff (7, 8) have demonstrated that ordinarily most of the protein-bound or precipitable iodine of the serum (SPI) consists of the thyroid hormone, thyroxine.

Methods for the measurement of SPI have been developed (5, 9 to 12) and have been intensively employed in a number of clinics It appears to be the most reliable criterion of thyroid activity that has thus far been utilized for the analysis of diseases and disorders of the thyroid gland (5, 11 to 19). In normal persons, SPI lies between 3 0 and 7 2 μg per cent, with occasional

[1] This review covers approximately the period from 1945 to 1950 References previous to 1945 have been inserted chiefly for background

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but no specific quantitative technique for thyroxine has, as yet, been reported.

In addition to these obviously artifactual aberrations, SPI is affected by certain physiological and pathological disorders unassociated with other evidences of disturbed thyroid function. In the nephrotic syndrome, advanced cirrhosis of the liver, and certain other diseased states associated with malnutrition, low values are frequently encountered These were, at first, connected with hypoalbuminemia (30), but this connection appears to be merely coincidental (20, 31). In the first 24 to 48 hr. after serious operations, SPI drops sharply, 1 to 3 μg per cent (21). Presumably this is a feature of the general reaction to injury; but the depression of SPI is more transitory than the hypoalbuminemia and hypolipemia that also occur after operations, lasting usually only 2 or 3 days.

SPI rises early in pregnancy to concentrations frequently so high that in the nonpregnant woman a diagnosis of hyperthyroidism would be warranted After 16 weeks, SPI usually exceeds 6 μg per cent and may be as high as 10 μg. per cent without evidences of abnormal thyroid activity (33, 34). It remains at these levels throughout pregnancy, falling at a variable rate after delivery. There is some evidence that failure of SPI to rise results in miscarriage, which may possibly be prevented by timely administration of thyroid substance The increment of SPI is extractable by butanol and is presumably thyroid hormone (21, 29).

With all these defects, measurement of SPI is a far more effective means for the determination of the activity of the thyroid gland than any other generally applicable procedure. It has proved valuable in the detection of hypothyroidism secondary to deficiency of the anterior lobe of the pituitary gland (31). The principal advantage it has over other tests, however, is its applicability to patients suffering from complicating conditions which interfere with the determination or interpretation of basal metabolism or serum cholesterol (32) In order that its full value may be realized, the effect upon SPI of diseases and disorders not connected with the thyroid must be further explored. Measurement of SPI has not been widely adopted because of the technical difficulty of the procedure This is one of the marks of the failure of clinical chemistry to achieve the dignity required if it is to realize the full benefits of advances in medical science. At the same time efforts to find a more specific method for the direct measurement of the thyroid hormone in serum should be continued. For this purpose extraction with butanol appears to be a promising point of departure.

Radioactive iodine (I^{131}) —Further reports of the use of tracer doses of radioactive iodine (I^{131}) appeared in the past year (35 to 48). The procedure has proved invaluable in the elucidation of certain physiological problems, and its utility in the differential diagnosis of thyroid disorders has been established This reviewer does not, however, share the enthusiasm of his predecessor (23) for its general adoption as a routine clinical procedure The use of radioactive isotopes, even in tracer doses, can not be safely en-

values between 7.2 and 7.8 μg. per cent. In hypothyroidism, it is less than 3.0, usually less than 2.0 μg per cent. In hyperthyroidism, it is usually above 7.8 μg. per cent; occasional values may be as low as 7.2 μg. per cent (20) While the SPI values of the members of any group of normal individuals differ from one another within the range defined above, the SPI of any single individual in good health is remarkably constant over long intervals (20, 21, 22). SPI seems to mirror accurately changes of thyroid activity in patients with uncomplicated disorders of thyroid function (5, 12 to 19).

Aberrations of SPI not related to thyroid activity have been discovered. Some of these are artifactual. Certain organic compounds containing iodine attach themselves to proteins firmly enough to be included in measurements of SPI. Chief among these are dyes employed for x-ray visualization of the gall bladder, urinary tract, and blood vessels. Iodized oil (Lipiodol) may also contaminate SPI (23, 24). Mercury, on the other hand, forms insoluble salts with iodine and, therefore, prevents its recovery by distillation. Consequently, so long as this metal is circulating in the blood (for example, for a short time after the administration of mercurial diuretics) analyses of serum for SPI will yield low values (21).

Of a somewhat different nature are falsely high values found after the administration of inorganic iodine and certain other drugs It has been shown by Danowski and associates (25) that, after the administration of large amounts (enormously greater than therapeutic doses) of iodides, not only the inorganic iodine, but also SPI, becomes considerably elevated. Slight elevations were noted after even therapeutic doses of iodine (26) After prolonged administration of large doses of thiourea or propylthiouracil with therapeutic doses of iodine, SPI may rise to concentrations altogether unrelated to any other evidences of thyroid activity. Under these circumstances, values as high as 10 μg per cent have been observed in myxedema and 70 μg. per cent in hyperthyroidism (27). These extreme anomalies appear to be transitory.

These artifactual aberrations of SPI have led to the search for a more specific means of separating hormonal from other types of iodine. Extraction of serum with butanol, followed by alkaline washing, and employed for a somewhat similar purpose by Taurog & Chaikoff (7), has been tested This procedure does not take up inorganic iodine, but does extract and retain thyroxine Fractions of some other organic iodine compounds, such as diiodo- and monoiodo-tyrosine, may also be retained by butanol (8). In addition, some thyroxine may be destroyed by washing with alkali (28). Nevertheless, in the serum of normal persons and of patients with untreated thyroid disorders SPI and butanol-extractable iodine do not differ appreciably (21, 25, 26, 29). The increments of SPI produced by administration of iodide (25) and apparently those that occur in the course of treatment with thio-drugs and iodine (21) are not soluble in butanol It is possible, therefore, that iodine extractable by butanol may be more specific than SPI as a measure of hormonal iodine. Chromatographic analysis of serum has been attempted (8),

cance of these distortions is apparent only when precise methods of analysis are employed. They are not confined to the cholesterol fractions, but involve also the ratio of cholesterol to phospholipid.

Cholesterol and atheromatosis—Because cholesterol esters are found in atheromatous lesions (67) and because the administration of cholesterol to rabbits causes hypercholesterolemia and abnormal depositions of cholesterol in the aorta, this essential compound has fallen into disrepute. The reaction of the rabbit to cholesterol is a peculiarity of this species mysteriously linked with activity of the thyroid gland (68). Other animals, including man (55, 69 to 71), appear to dispose of administered cholesterol with great facility. It has been shown that if dogs are rendered hypothyroid, this capacity is reduced (65, 66, 72 to 74) Injury to the aorta also conduces to deposition of cholesterol when it is administered in large quantities with or without thiouracil (74) There is no good reason to believe that atheroma of man is related to hypothyroidism.

Recently, Morrison (75, 76) and others (77) have claimed that there is a statistical relation between hypercholesterolemia and coronary disease. In these studies, however, the statistical difference depends upon a preponderance of high values for serum cholesterol in the figures from coronary cases, which also include values as low as any found in normal subjects As Morrison and associates (75) have pointed out, this may mean that certain groups or types of subjects with hypercholesterolemia have a susceptibility to atherosclerosis and coronary occlusion. That there is such a condition among persons with familial lipemia, the disease which also gives rise to xanthomatosis tuberosum, has been established (70, 78 to 80), although the susceptibility to atherosclerosis even in families with this diathesis appears to be variable 81, 82, 83) The frequency of this condition seems to have been underestimated Emphasis has been placed also on the variability of cholesterol in patients with coronary occlusion (76) This is, however, a characteristic of disease in general and can, therefore, be evaluated only by a careful analysis of associated disorders Although attention has been centered on hypercholesterolemia in familial lipemia, actually the phospholipids are increased as much or more than cholesterol (63, 77, 81) This is only one illustration of the need to include other lipid fractions in analyses of clinical conditions. Efforts have been directed to the use of diets which will reduce the concentration of cholesterol in the serum Even in familial lipemia, however, it has been found that serum cholesterol is peculiarly unaffected by the quantities of fat or even cholesterol eaten (63, 70, 82, 84, 85) It is doubtful whether it would be an unconditioned blessing to lower the serum cholesterol of an individual by dietary measures. Serum cholesterol does fall after injury (86) or in malnutrition (87, 88), especially malnutrition associated with specific deficiencies. In animals and presumably in man, it is a characteristic accompaniment of most types of dietary fatty liver, a condition that, with its unhappy sequelae, is not necessarily preferable to potential arterial disease. Choline and other lipotropic substances appear to have no effect on the hyper-

trusted to inexpert hands without adequate facilities. Besides, the technique is inapplicable to the clinical appraisal of thyroid activity at intervals over long periods, which is an essential part of the proper management of patients with thyroid disorders For this purpose, chemical analysis of the serum is far more suitable.

The Serum Lipids

Most clinical—and indeed physiological—studies of lipid metabolism, even for investigative purposes, are limited to measurement of the concentration of cholesterol in the serum This has little more than symbolic value When, for further simplification, the Liebermann-Burchard colorimetric procedure is applied to simple extracts of serum, even the symbolic value of the results is open to question Precipitation with digitonin and isolation of the precipitate are essential prerequisites to the determination of cholesterol. Methods have been devised for the precise measurement of the precipitated cholesterol either colorimetrically (49 to 52) or gravimetrically (53). While the concentration of cholesterol is quite constant over long periods in the same individual (54 to 57), the range of variation among the members of any group is large, from 150 to 300 mg. per cent; abnormalities can only be recognized when they are gross, therefore, unless the concentration characteristic of the individual is known The relations of the various lipid components to one another is quite consistent and independent in health and many pathological conditions of the total concentrations of lipids. In the serum of normal persons, the proportion of cholesterol in the free state varies only from 24 to 32 per cent regardless of the concentration of total cholesterol (58, 59). The ratio of phospholipid to cholesterol is equally constant (59 to 64). Because of the constancy of the proportions of lipid constituents, the concentration of cholesterol is ordinarily an index of the concentrations of all lipid components. It is this consistency in the interrelationships of the lipid fractions that has tempted clinicians and physiologists to use cholesterol as a measure of lipids in general

In the past, cholesterol has been used as an aid in the diagnosis of thyroid disorders Its value for this purpose is, however, quite limited It is usually elevated in uncomplicated hypothyroidism, but the effect of thyroid deficiency may be modified by a variety of other conditions (60) A possible explanation for these anomalies has been found by Entenman, Chaikoff & Reichert (65, 66). Apparently, removal of the thyroid gland renders the serum lipids of an animal susceptible to the effects of diet. In hypothyroidism (60) and in the nephrotic syndrome (62) in which hyperlipemia is also encountered, the normal relations of free and total cholesterol to one another and to phospholipids is preserved; but in the nephrotic syndrome, neutral fat rises, while it is unaffected in hypothyroidism. In diseases of the liver, on [illegible]

diseases of the liver (97), these estimations can be made with a reasonable degree of assurance. Even in normal persons, the concentration of neutral fat is more capricious than that of the other lipid components with which it does not seem to be correlated (59 to 62, 64). The significance of its vagaries and their relation to visible lipemia and lactescence merit further investigation by precise methods, preferably those that measure the fatty acids stoichiometrically.

The physical state of the lipids has recently attracted renewed attention because of improved methods of observation. The studies of the distribution of lipids between protein fractions has already been mentioned In the somewhat emotional interest in coronary disease and the failure to relate atheroma directly with serum cholesterol, efforts have been made to connect it with the physical state of the serum lipids Becker, Meyer & Necheles (98) have reported that after a standard fat meal of 0.5 gm. of oleomargarine per kg, the chylomicron counts in the sera of elderly persons rise higher and remain elevated longer than those of young persons. Gofman and associates (99), by ultracentrifugal technique, have discovered in sera a class of large lipid molecules of low density containing approximately 30 per cent cholesterol, but little or no protein. These appeared to be more plentiful in the sera of males than females; they increased in frequency with age and were particularly conspicuous in persons who had suffered coronary occlusions. They also appeared to be more frequent in the sera of diabetics Such statistical relations are open to the same objections raised earlier to similar treatment of chemical determinations of cholesterol, despite the novelty of the technique and the dramatic nature of the correlation. Even if this correlation should prove more precise than others, its exploitation will require investigation of its significance with respect to lipid metabolism.

Fecal fat—Quantitative examination of feces for other than investigative purposes has been neglected in the clinic, chiefly for esthetic reasons. With modern "blenders," mixers, and homogenizers, some of the objections to such analyses have been removed The importance of measuring fat and nitrogen of feces in the differentiation of diarrheas has been demonstrated. Van de Kamer, ten Bokkel Huinink & Weyers (100) have recently published a method by which the fat in a homogenized stool can be determined with accuracy and relative ease within 45 min.

PROTEINS OF THE SERUM

Indirect methods, and especially the copper sulfate specific gravity technique of Van Slyke *et al.* (101, 102), for the measurement of serum proteins filled a crying need in the war where facilities and time were limiting factors. They are not appropriate for a well-ordered clinic with proper facilities because they give falsely high values in the presence of hyperglycemia or nitrogen retention and because they do not permit fractionation of the proteins, which is essential for the evaluation of protein concentrations. For the actual measurement of protein and its fractions, the Kjeldahl method still remains

cholesterolemia of patients with hereditary lipemia (63, 70) or coronary disease (76), although they seem to prevent (89) or even reverse (90) the cholesterol atheromatosis of rabbits. The difference is probably referable to the fact that in the latter, the atheromatosis is only part of a general disorder of lipid metabolism which includes fatty liver (68, 91).

The physical state of the serum lipids.—Under ordinary conditions, plasma is a limpid solution although it contains about 0.4 to 0.8 per cent of lipids that are insoluble in water. It has long been recognized that the apparent solubility of the lipids in plasma depends upon their attachment to the proteins, since they are precipitated with the latter by the precipitants commonly used and can be extracted from the precipitated protein by appropriate solvents. It has now been demonstrated that this vehicular function is not a common property of all the protein fractions, but adheres particularly to the α- and β-globulins or to components of these groups (92 to 96). In the dog, α-globulin carries the larger load, while in man it is borne chiefly by the β-fraction (94, 95). The distribution of the lipid load may be disturbed by disease (96). Discovery of the forces which determine the distribution of this load should aid in the resolution of the mystery surrounding the transport of the lipids. In spite of the fact that the major part of ingested lipid is rapidly absorbed and delivered via the lymph from the thoracic duct *en masse* into the systemic blood stream, the concentrations of lipids in the serum of normal individuals are surprisingly little affected by meals or by other activities that must involve large transfers through the blood stream.

In addition to the lipids firmly attached to proteins, there appears to be a small fraction in a more or less free state. Under certain conditions and in certain diseases, this may increase to such an extent that the fatty material separates like cream when the serum is chilled. Sometimes it imparts a definite lactescence to the serum at room temperature or even at the temperature of the body. Although in these extreme cases, there is usually a coexistent hyperlipemia, the gross visibility of lipemia is not directly correlated with the concentration of lipids in the serum. In its more subtle forms, this disturbance of state of the lipids may be discerned by special optical techniques. Chylomicrons, microscopically visible lipid particles, increase in the serum after meals (or perhaps, more precisely, after a fatty breakfast) when moderate lactescence is also not uncommon. Lactescence of a gross type is most strikingly encountered in diabetic acidosis, the nephrotic syndrome, some forms of liver disease, and hereditary lipemia. These conditions have one common feature: in all, the concentration of neutral fat in the serum is abnormally high. It is more correct, perhaps, to say that the ratio of fatty acid to cholesterol esters and phospholipids is abnormally high since the concentration of neutral fat can be estimated only by difference as the fatty acid not accounted for as cholesterol esters or phospholipid. Such an accounting involves certain assumptions concerning the nature of the phospholipids. Since recent investigations have generally agreed that the proportion of choline-containing lipids in the serum is quite constant, even in

sium in serum and other biological fluids has become a practical clinical procedure There are a number of suitable instruments on the market, but the literature on their application and behavior is extremely scanty. So laborious and time-consuming were analyses for sodium and potassium in the past that they were useful only for investigative purposes or for retrospective consideration. For diagnostic purposes or the control of therapy, serum sodium had to be estimated from chloride—or better, chloride plus bicarbonate—with the aid of inference. Direct measurements of sodium on large numbers of patients with various diseases and disorders have proved that such estimates and inferences were not highly reliable and that the concentration of undetermined anions, Na-(Cl+HCO_3), is more variable than had been supposed (115, 116). Since sodium is a measure of the osmotically active electrolytes of the serum, knowledge of its concentration is of the utmost importance in the regulation of the equilibrium of salt and water in the body. Its measurements should not, however, become a substitute for, but a supplement to, determinations of chloride and bicarbonate. Knowledge of the concentrations of these three ions provides the data necessary for the evaluation of both osmotic and acid-base equilibria. In a well-organized clinical chemical laboratory, it should be possible, in case of emergency, to secure this information within an hour or less so that it can be made available in advance of or early in the course of therapy.

More frequent determinations of serum potassium have disclosed the somewhat surprising fact that potassium deficits are far commoner and more significant than the excesses that had been feared (119) Such deficits are especially prone to develop in conditions in which there has been wasting, especially when this is associated with loss of gastrointestinal secretions Among the conditions in which they have been described most frequently are diabetic acidosis (118 to 123), diarrhea (124 to 127), and vomiting (128, 129). They may be encountered even in the presence of severe renal insufficiency (129, 130) They are most likely to appear when dehydration and starvation are overcome by administration of fluids containing sodium chloride and carbohydrate, for example, during recovery from diabetic acidosis The depression of serum potassium under these conditions results from expansion of the extracellular fluid, accelerated excretion, and movement of the ion into cells (122, 123). This last process is probably connected with resumption or acceleration of carbohydrate combustion, although it may be aided by rectification of the concentration of sodium in the extracellular fluids

Volumes of Body Fluids

Methods have been devised for the estimation of the volumes of various fluid compartments of the body All of these methods depend on the general principle of measuring the concentration in the serum of some test substance that has been injected into the blood stream after sufficient time has elapsed to permit the substance to become uniformly distributed throughout the

the standard procedure. It has been amply demonstrated by comparisons with electrophoresis that the Howe method of salting out protein fractions, which has been widely adopted as the standard technique, does not separate albumin from globulin precisely, including with the former a large proportion of the α-globulins. The latter tend to increase in most conditions in which albumin is depleted The Howe method, therefore, fails most signally when precise information is most desirable. Electrophoresis is not suitable for routine clinical analyses because it is so time-consuming and so ill-adapted to multiple measurements Furthermore, although it is an elegant procedure, it has not the infallibility generally attributed to it because it measures with the proteins the lipids attached to them.[2]

A number of methods have been devised by which albumin and globulin and globulin fractions can be separated chemically with precision. For this purpose, Pillemer & Hutchinson (103) employ methanol. The procedure is adapted only to the separation of albumin from globulin and must be conducted at temperatures near freezing. Bing (104) and others have for many years used the technique of Henriques & Klausen (105) in which precipitation is effected by a mixture of sodium and potassium sulfates Bock (106) has reported that it gives values for serum albumin that agree with those obtained by the method of Pillemer & Hutchinson. Majoor (107) showed that by a modification of Howe's principle, not only albumin and globulin but also the fractions of globulin could be differentiated by salting out with sodium sulfate Milne (108) and Kibrick & Blonstein (109) have shown that values for protein fractions by Majoor's principles agree with those obtained by electrophoresis. Cohn & Wolfson (110) have presented a method for the partition of albumin and globulin by sodium sulfite that meets the same criteria With these new procedures available, the Howe and similar techniques that give inaccurate partitions should be abandoned. This will necessitate the revision not only of standards for the concentrations of protein fractions, but also of formulae which have been proposed for the estimation of colloid osmotic pressure, calcium bound to protein, etc , from concentrations of protein fractions It has been conclusively demonstrated that a variety of empirical tests for liver function, such as the Takata-Ara and cephalin-flocculation tests, are quite nonspecific and depend chiefly upon derangements of the patterns of proteins in the serum. Although the utility of these tests can not be disparaged, they should not, because of their convenience, become a substitute for accurate chemical measurements of protein or lipids and their fractions in the serum Jager & Nickerson (111) and Kunkel *et al* (112) have described methods for the separate measurement of γ-globulin

Flame Photometers

With the development of a simple and suitable flame photometer by Barnes, Berry and associates (113, 114) measurement of sodium and potas-

[2] The nitrogen of phospholipids is, of course, included in Kjeldahl analyses, but the error from this source is comparatively small

maintained for 24 hr. or longer (144), conclusive proof that at least the tagged red cells do not escape from the circulation nor become trapped in inactive portions of the circulation. If uneven distribution of red blood cells does vitiate the use of tagged cells for the measurement of blood volume, there is as yet no precise measure of this function Even if the use of cells tagged with radioactive iron were open to no question, its application would be extremely limited because it requires prepared donors. Iron can be incorporated in red blood cells only *in vivo*

Radioactive phosphorus, P^{32}, has been proposed (149, 150) as a more practical substitute, since phosphate can be introduced into red blood cells *in vitro* (151). Exchange of phosphate between cells and plasma is ordinarily such a slow process that it is negligible in the short period required for measurement of blood volume. Values obtained by P^{32} and by radioactive iron agree in most instances (152); but in particular individuals in all series, blood volumes measured by P^{32} are too large, presumably because the discharge of cellular phosphate is accelerated by some metabolic disturbances (150 to 153).

Extracellular fluid—For the measurement of the extracellular fluid, a large number of substances have been employed The majority of those which appear to be most specifically confined to this compartment are excreted by the kidneys with great rapidity, usually chiefly or entirely by glomerular filtration For this reason, it is almost impossible to establish a uniform concentration of the test substance throughout the extracellular fluid in equilibrium with its concentration in the water of serum (154). This difficulty is enhanced if the extracellular fluid is expanded by edema, particularly if it is segregated in pools in serous cavities (154). It is also exaggerated if the test substance diffuses slowly In addition, some of the substances used for measurement of the extracellular fluid (e g , mannitol, sucrose, and sulfate) have a diuretic action They, therefore, tend to alter the function they are intended to measure To avoid the errors attendant upon failure to attain equilibrium between serum and extracellular fluids, it has been suggested that the extracellular fluid be estimated from the quantity of test substance excreted after a constant concentration of the substance in the serum has been established by continuous intravenous injection. Inulin and mannitol have been utilized for this purpose (155, 156). With such a rapid rate of urinary excretion and such a slow rate of diffusion, especially when inulin is used, it is doubtful whether equilibrium can be attained in all cases within a reasonable time even by this technique (157, 158). Even if equilibrium is attained, the procedure is so time-consuming that it can not be used to measure the volume of extracellular fluid for clinical purposes nor to study rapid changes of this volume. Besides these limitations, it requires the injection of a considerable volume of fluid, which alters the volume of extracellular fluid Certain test substances, of which mannitol is an example, by their osmotic effects may alter the distribution of fluid between the intra- and the extracellular compartments (159). It does seem to have been

body of fluid to which it has access The quantity of substance in the body divided by its concentration in the serum, will, if such a state of equilibrium has been attained, give the volume of fluid through which it is distributed A proper correction must be applied for the quantity of the substance that may be destroyed or excreted in the course of the test. The precision of any such measurement depends first on the degree to which the test substance is confined to the particular fluid compartment under consideration. If it is not completely restrained therein or if it is destroyed or excreted, means must be found to evaluate the magnitude or rates of these disturbing factors Secondly, there must be certainty that equilibrium, that is uniformity of concentration in the water of serum and all parts of the fluid compartment, is attained Unfortunately, the methods available without exception fail to meet these requirements to variable degrees. Furthermore, although they have served useful purposes in physiological and clinical investigations, they are not for the most part suitable for control of therapy.

The circulating blood and plasma—The use of the blue dye, T1824, for the measurement of the volume of the circulating plasma is open to objection because this compound escapes from the blood stream to appear in the thoracic duct lymph, by which a part may again return to the circulation. For this reason alone, it must yield excessive values. Whatever argument there may be about the magnitude of this error, it can not be dismissed altogether and is presumably variable Correction by extrapolation to the time of injection on the removal curve (the curve describing the diminution of the concentration of the substance in the serum after apparent equilibrium has been reached) is unsatisfactory because it has been repeatedly demonstrated that the initial portion of this curve is highly complex (131 to 135). Whereas equilibrium is reached with tagged red blood cells within the space of about 4 min. (132, 133, 136), the time required to attain a steady rate of removal of T1824 is four or five times as long. The vagaries of the initial curve are not, therefore, merely a product of mixing The use of carbon monoxide to tag red blood cells yields values for blood volume that, on the average, agree with those obtained with T1824 (137, 138) Evidence has, however, been adduced that carbon monoxide may be oxidized to some extent in the body (139, 140, 141).

Red blood cells tagged with radioactive iron regularly yield smaller values for blood volume than dyes do (142 to 145). This has been attributed by some to unequal distribution of cells and plasma in the circulating blood, although evidence on this point is not clear (142 to 144, 146) Whatever may be the magnitude of this error, it will not eliminate nor cancel the error of the dye method. There is no mathematical justification for the proposal by Gibson *et al.* (147, 148) and others that the dye method be used for the estimation of plasma volume and the radioactive cell method with a corrected hematocrit, for the estimation of cell volume, the sum of the two being taken to represent the total volume of the circulating blood. This is only compounding errors. With radioactive cells, equilibrium is obtained within 4 min. and may be

maintained for 24 hr. or longer (144), conclusive proof that at least the tagged red cells do not escape from the circulation nor become trapped in inactive portions of the circulation. If uneven distribution of red blood cells does vitiate the use of tagged cells for the measurement of blood volume, there is as yet no precise measure of this function. Even if the use of cells tagged with radioactive iron were open to no question, its application would be extremely limited because it requires prepared donors Iron can be incorporated in red blood cells only *in vivo*

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established by means of these techniques that the volume of extracellular fluid in normal persons has been overestimated in the past. It is probably smaller, rather than greater, than 20 per cent of the body weight (156).

Sulfocyanate continues to be used because it can be given orally and because it is excreted slowly. This substance is definitely not confined to the extracellular fluid Even in normal persons, it penetrates red blood cells and enters gastrointestinal fluids It has recently been demonstrated that in some diseases, it becomes even more widely distributed (160, 161).

Because muscle cells contain inappreciable amounts of chloride and because this ion has a smaller volume of distribution than sodium, it has been used, at the suggestion of Darrow (162), as a general criterion of changes of the volume of extracellular fluid and to estimate transfers of sodium and potassium between this fluid and the cells, despite the knowledge that certain tissues, among them the liver, contain proportionally more chloride than sodium. In the intact animal, such estimations based on balances of sodium, chloride, and potassium and the concentrations of these ions in the water of serum must be made with considerable reserve Not only may chloride enter or leave these tissues in the course of a study, but it may be discharged selectively into the stomach or absorbed with the same selectivity in large quantities from the gut

Total body water —For measurement of the total water in the body, heavy water appears to be the most suitable test substance (163, 164) It diffuses with great rapidity Because it mixes completely with all the water of the body and is excreted with normal water in proportion to its concentration, the elimination in the urine of the small quantities required for the measurement of body water is quite slow. Equilibrium can, therefore, be established within a reasonable time Deuterium oxide is not an ideal substance for the measurement of body water because it is not altogether inert. Water enters into all kinds of chemical (especially hydrolytic) reactions Ultimately, deuterium may become incorporated in most of the organic compounds of the body. Since the quantity of deuterium oxide given is so small in proportion to the total water, however, the degree to which it is utilized in the short interval required for determination of its volume of distribution is almost negligible It has been employed for the measurement of the total body water of humans by some observers (165, 166, 167)

Soberman, Brodie *et al* (166) have proposed the use of antipyrine for the measurement of total body water. This compound, like alcohol, appears to diffuse freely throughout all the water of the body, traversing all membranes including those of the renal tubular epithelium Its concentration in urine and serum are, therefore, identical It is consequently excreted extremely slowly It does not, however, meet all the other criteria for an ideal measure of total body water The major part of the compound is destroyed in the body or excreted in some other form Although the rate of disappearance is slow and consistent in normal persons, it has not been established with certainty that it may not vary in pathological states There is some evidence

that the site of destruction may be the liver which seems to take up more of the compound than other organs do Finally, a fraction appears to combine with the serum proteins. In the aggregate, these properties, especially the combination with proteins, constitute serious objections to antipyrine as a measure of body water. It may, however, prove a useful instrument. Values for total body water estimated from the volume of distribution of antipyrine are slightly, but distinctly, smaller than those obtained with deuterium oxide (166). Measurements by both methods indicate that the volume of water in the bodies of normal men and women have been overestimated in the past, being nearer 60 per cent, or even less, of the body weight, instead of 70 per cent (166).

Renal Clearances

Information of the greatest value has been obtained by means of measurements of renal clearances In fact, a large part of our knowledge of the details of renal function has been derived or verified by means of these techniques Nevertheless, even the simplest of them is ill-adapted to routine clinical use because all demand such meticulous attention to detail. The most painstaking accuracy in chemical analyses is utterly wasted if there is any error in the timing and collection of specimens of blood serum or urine. The latter is at all times somewhat uncertain; the uncertainties are exaggerated by diseases, especially those of the urinary tract. Insertion of a catheter, especially an inlying catheter, is not an innocent procedure· If these technical difficulties are surmounted, clearances are elegant comparative measures of renal disability in disease. On the other hand, they can not be used with the same confidence as precise measures of particular functions of the kidneys.

A great variety of substances have been proposed for the measurement of glomerular filtration The clearances of these substances are nearly identical, and when any two are employed simultaneously, they vary proportionally, but in no studies are identity and proportionality consistently as precise as the estimated accuracy of the methods themselves should require So capricious are these deviations that it is impossible to deny that they may be products of technical error; but the possibility can not be excluded that the tubular epithelium is not consistently indifferent to these test substances, that small fractions may be regularly or under special conditions secreted or reabsorbed Inulin has many properties to recommend it as a measure of glomerular filtration and has, almost by common consent, been accepted as the yardstick for the evaluation of purely filtrable substances, but some of the evidence on which its use for this purpose is based is purely inferential Robson, Ferguson *et al* (168, 169) have recently adduced evidence that as much as 15 per cent of the inulin that passes through the glomerular filter may be reabsorbed from the renal tubules They have also directed attention to the fact that clearances of inulin, like those of exogenous creatinine and certain other substances, vary according to the conditions under which they are measured, diminishing when the concentration of inulin in the serum is

established by means of these techniques that the volume of extracellular fluid in normal persons has been overestimated in the past. It is probably smaller, rather than greater, than 20 per cent of the body weight (156).

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paragement, but to call attention to the need for discrimination in their application and interpretation. Such indirect measurements, which involve the intermediation of physiological functions, can not have the specific significance of direct chemical analyses. They can not be interpreted with the same rigor, but must be tested by other procedures and by astute inference It follows also that they can not be proved by normal controls alone; they require also analogous controls.

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falling. Clearances of substances that are secreted or reabsorbed by the tubules are subject to disturbance by other factors not connected with the function they are intended to measure. For example, the secretion of *p*-aminohippurate (PAH), which has been widely used for the measurement of renal plasma flow may be influenced by the reabsorption of glucose (170, 171). Its secretion is also reduced by the mercurial diuretic, mersalyl (Salyrgan) (172).

Substances which are used to measure either filtration or renal plasma flow are excreted with such rapidity that when changes of these functions over any long period are under investigation, it is necessary to inject the substances continuously with considerable volumes of fluid. The discomforts of such procedures as well as the introduction of such volumes of fluid can not be neglected in the evaluation of the clearances The addition to these solutions of other solutes, such as sodium chloride, or the use of diuretic substances, such as mannitol, further complicate interpretations. For these reasons, clearances of endogenous creatinine, though analytically less precise, are frequently to be preferred.

These errors, however, sink into insignificance when compared with those that may enter when these clearance techniques are applied to the analysis of glomerular and tubular functions in diseases or disorders in which the integrity of the tubular epithelium has been compromised. The use of substances for the measurement of renal plasma flow or glomerular filtration is predicated upon the impermeability, or at least a relative and constant degree of impermeability, of the tubular epithelium to these substances. When this impermeability is impaired by injury of the tubular epithelium, the test substances, becoming concentrated in the tubular lumina, will diffuse back into the renal tubules and vessels. This was first illustrated in the classic experiments of Richards (173) on the behavior of phenol red in the kidney poisoned by mercury. A similar phenomenon was demonstrated with respect to creatinine (174) in dogs who had been poisoned by uranium. Several articles have appeared recently in which direct measurements of renal blood flow or the removal of PAH from the blood passing through the kidney have been compared with the renal plasma flow estimated from renal clearances of PAH in acute renal failure (lower nephron nephrosis) and other conditions attended by injury to the tubular epithelium In these conditions, it has been found that, because of back-diffusion, renal clearances greatly underestimate renal plasma flow (175 to 178) Presumably, measures of filtration by clearance techniques in these conditions are equally faulty Arguing by the *reductio ad absurdum*, it must be obvious that if lower nephron nephrosis is reparable, temporary anuria can not denote complete cessation of the blood [illegible] that glomerular filtration [illegible]e nil. A recent article by [illegible]pplicability of renal clear-

Attention has been called to these weaknesses of available methods for the measurement of body fluids and renal function, not in a spirit of dis-

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DISEASES OF THE SKIN[1]

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Introduction

This chapter reviews recent advances in selected areas of dermatology with stress on those disorders of the skin associated with internal and systemic disturbances. Modern dermatology finds itself fusing with internal medicine, and conversely, internal medicine is turning to and learning from the skin It becomes constantly more evident that there are relatively few dermatoses in which the disturbance is limited to the skin, and consequently, study, diagnosis, and treatment involve more than looking at the skin and applying something to it. No attempt is made to cover the entire field of dermatology, and space limitation precludes systematic coverage of the literature on those subjects included. Subjects discussed are vitamin A metabolism, porphyria and photosensitivity, localized myxedema, acne vulgaris, hair, roentgen therapy, bacterial infections, psoriasis, pemphigus, disseminated lupus erythematosus, chloramphenicol in virus infections, calciferol in treatment of lupus vulgaris, and adrenocorticotrophic hormone (ACTH) and cortisone.

Metabolic Disorders

Vitamin A.—In the twenty years since the fundamental paper of Frazier & Hu (1) appeared, the subject of vitamin A in dermatology has become of major importance. A large number of apparently unrelated cutaneous syndromes and clinical disorders have been shown to respond to vitamin A therapy, and at present, we seem to be on the verge of a great synthesis in which this group of disorders can be brought together as morphologic variants of the same basic disease—namely, abnormal keratinization due to disturbed vitamin A metabolism. (We would like to suggest the phrase "vitamin A failure" rather than "deficiency," since many of these syndromes occur in the presence of adequate diet and apparently normal blood levels of vitamin A, and because there is increasing evidence that the error may be in assimilation, utilization, storage, release, etc. Vitamin A dietary deficiency is rarely the cause of the difficulty) Included are ichthyosis, pityriasis rubra pilaris, keratosis follicularis (Darier's Disease), pachyonychia congenita, keratoderma palmaris et plantaris, phrynoderma, xerosis, lichen spinulosus, porokeratosis, and a large group characterized by hyperkeratosis of the pilosebaceous orifices, such as keratosis pilaris, lichen lividus, ichthyosis follicularis, etc.

[1] This review covers approximately the period from January, 1948 to September, 1950.

Frazier & Marmelzat (2), in a fine retrospective study of the literature from Willan to the present, have shown that most if not all of the disorders listed above are in fact morphologic variants of the same disease. They state:

> As one threads . . . through the varied literature . . . one finds that the confusion and christening and rechristening of similar diseases in large measure depended merely upon the chance variations in distribution, elevation and shapes of follicular lesions, upon the ease with which the follicular plugs could be dislodged, and on what type of residual scarring eventuated—all of no importance within themselves. Many times the same case is claimed under various names by different dermatologists

Although in this particular comment Frazier & Marmelzat were referring to the follicular hyperkeratoses, the same might well be applied to all of the primary hyperkeratotic diseases

It should be noted that most of the "diseases" listed above have been previously classified as "nevi," i e., a congenital and developmental structural defect. Furthermore, prior to the use of vitamin A in their treatment, most were considered incurable. It is of interest now to consider that they may, in fact, be based upon an hereditary defect, but that the defect is initially physiologic and metabolic, not structural. A strong case can be made for the thesis that they represent an inborn error of metabolism genetically transmitted. In this connection, it is worthwhile to recall the prophetic clinical judgment of Wilson (3), who, in 1878, in discussing one of the forms of follicular hyperkeratosis which he called "folliculitis rubra," said:

> The cause of this state of the skin is, essentially, defect of nutrition power operating in congenital and sometimes hereditary weak skin. I was much struck with the presence of this affection in a family of three or four young ladies, the daughters of a gentleman who I knew to be the subject of ichthyosis, with which defect of the skin folliculitis rubra is closely aligned.

Thus far we have been concerned with what might be called the primary dyskeratoses There is another group of disorders in which hyperkeratosis occurs as a sequential or concommitant phenomenon, and in these also vitamin A therapy is often of great value in correcting the hyperkeratotic component The more important in this group are senile keratoses and the keratoses of chronic actinic dermatitis, acne vulgaris, keratoderma climactericum (Haxthausen's syndrome), abnormal callus formation, leukoplakia of the buccal mucosa, kraurosis vulvae, and others.

The medical treatment of senile and actinic keratoses represents a major step in the prophylaxis of skin cancer, numerous observers having reported excellent results The reviewers' own unpublished experiences are in agreement. A recent report [Savitt & Obermayer (4)] is representative. They report results on 11 patients with well-developed senile keratoses treated with 150,000 units of vitamin A in oil daily Duration of treatment varied from 6 to 18 months Four of the eleven showed no response, the other seven had substantial improvement. It should be noted that satisfactory results are not obtained in all cases, and this is true in most of the syndromes under

discussion This raises certain as yet unanswered questions concerning individual differences in absorption, utilization, type of preparation administered, hepatic function, and other links in the chain of vitamin A metabolism These will be considered later

Still another group are the individuals with "dry" skin, mild degree of xerosis, who because of this are susceptible to infection and contact irritation and thus develop nonspecific eczematous dermatitis or lichen simplex chronicus. This group represents a numerically important problem in clinical dermatology.

With increasing interest in and recognition of vitamin A dysfunction, it is fortunate that great advances have been made in the past several years in the development of more efficient preparations (aqueous dispersions) for therapy. The result has been not only that more complete and rapid results can be obtained, but that cases which did not respond to vitamin A in oil in many instances show satisfactory response to the newer emulsion and water-soluble preparations Since the absorption of the new preparations is many times more efficient, therapeutic dosage levels are correspondingly reduced, thereby reducing the cost and frequency of administration and increasing the chances that the patient will take the medicine. It is also apparent that since so-called daily requirements were based upon studies with oily solutions, current standards will need revision.

Davidson & Sobel (5), studying vitamin A in the treatment of acne vulgaris, found (*a*) absorption was greater, (*b*) blood levels were higher, and (*c*) therapeutic response appeared earlier with aqueous dispersion as compared to oily solutions. They raise the important question that higher blood levels theoretically might be the basis for greater diffusion into tissue, plus the fact that the smaller particle-size of the vitamin A in aqueous dispersion may also account for better diffusion into the skin.

Their work as well as that of many others indicates that 25,000 to 40,000 units of vitamin A in aqueous dispersion may be as effective as 100,000 to 150,000 units in oily solution. Furthermore, it has been shown that the aqueous solutions are absorbed in satisfactory amounts in individuals with such disturbances as steatorrhea and pancreatic fibrosis [May & Lowe (6)]

Volk & Popper (7) report continued studies on the absorption of vitamin A and fat as determined by fluorescent microscopy. After feeding test doses to rats, sections are taken from duodenum, upper and lower jejunum, and ilium and fixed in formalin. Frozen sections are made, mounted in water, and examined by fluorescent microscopy. This permits determination of the tissue distribution of vitamin A and a rough measure of quantity. Tissues to be studied for fat are stained with Phosphine 3R.

Their findings confirm that vitamin A and fat are absorbed faster and in greater quantity when given in aqueous dispersion than in oily solution, the absorption with aqueous dispersion being three times as great. The route of absorption is via epithelial cell, to mesenchymal cells in the lamina

propria of the intestinal villi, thence to the lacteals. None is found in blood vessels. With the aqueous preparation, the greatest absorption occurs in the upper jejunum, whereas with the oily preparation, the major fluorescence was more often in the lower jejunum. Furthermore, the vitamin A fluoresence disappeared at a higher level in the intestine with the aqueous preparation.

The characteristics of aqueous dispersions as compared to oily solutions are summarized (8) as follows: (*a*) increased rate of absorption in children as measured by blood levels, in normals and with celiac syndrome, (*b*) increased liver storage in test animals (rats), (*c*) more efficiency in promoting growth in vitamin A deficient chicks, and (*d*) higher blood levels in premature and full-term infants, children, and adults The difference is apparently based on the greater intestinal absorption as indicated by fecal excretion

Since it appears that evidence of vitamin A failure or dysfunction is relatively common in the skin, it is surprising that it is not manifested more often in other tissues and organs, even admitting that the skin is most sensitive to deficiency states because of its characteristic rapid growth and replacement. Except for the field of ophthalmology, little attention is given to the subject. A recent report (9) on leukoplakia of the renal pelvis includes vitamin A deficiency as a possible etiologic factor. Higgins (10) reported that 40 per cent of patients with renal lithiasis have subnormal dark adaptation and recommended vitamin A in the therapeutic program Lobel (11) reported improved hearing in patients with progressive deafness following the use of parenteral vitamin A. Support of Lobel's results is found in 30 cases reported by Anderson and co-workers (12)

Marmelzat (13) has observed an eight-year old girl with keratotic follicular papules, renal calculi, localized corneal hyperkeratosis, and keratinized epithelial cells in the urinary sediment. Response to vitamin A therapy was definite.

The development of the clinical signs of vitamin A failure involves many weeks or months, and reversing the process is equally slow. In well-established syndromes, several months under therapy are required to show beginning improvement, and the maximum may not be achieved in less than 18 to 24 months, as in well-developed phrynoderma and ichthyosis.

Investigative work of concrete value has been carried out during recent years relative to important links in vitamin A metabolism. The evidence has been outstanding that the intestinal wall rather than the liver is the main site of the conversion of carotenes to vitamin A. This was first demonstrated by Sexton, Mehl & Deuel (14), who found that β-carotene given parenterally in the rat appeared in the liver as carotene, with no increase in vitamin A in plasma or liver, whereas vitamin A formation could be readily demonstrated by giving carotene orally This work has been confirmed by others, especially Mattson (15) and Krause & Pierce (16), the latter proving extrahepatic conversion of carotene in the normal rat by the following procedure: partial ligation of portal vein to promote collateral circulation, later

complete closure of portal vein, hepatic artery, and common bile duct, and then feeding of carotene. Blood taken 6 to 8 hr. later showed great increase in vitamin A comparable to that in normal rats fed carotene, but no carotene was found in plasma, proving extrahepatic conversion.

Since some instances of vitamin A failure may be on the basis of failure of carotene conversion, this mechanism is of great clinical interest. Among other factors which may influence this process is the role of thyroid function. Johnson & Baumann (17) present data that thiouracil and thiourea prevent storage of vitamin A in the liver when carotene is fed, but not when vitamin A itself is given, thus supporting evidence previously submitted (18).

The liver, nevertheless, represents the main storage depot of vitamin A and releases it to meet needs of the body Liver disease, through failure of storage or release, may lead to vitamin A deficiency as illustrated by the reports of Glazebrook & Tomaszewski (19, 20) In one instance, ichthyosis developed in Hodgkin's disease, in which liver disease was demonstrated clinically. The plasma vitamin A level was very low and could not be materially raised in spite of massive doses of vitamin A by oral and parenteral administration although there was a temporary clinical response in the skin. Their second case (with spindle-cell sarcoma) showed similar skin lesions, clinical and postmortem evidence of liver disease, and failure to respond to massive vitamin A therapy. Of particular interest was the fact that in the second case, more than 3 million units of vitamin A were found in the liver, indicating failure of release.

White and co-workers (21) have used plasma vitamin A levels as a test of hepatic function in the differential diagnosis of jaundice. In 92 cases in which jaundice was demonstrated clinically and by serum bilirubin and in which the final diagnosis was established by exploratory laparotomy, necropsy, or adequate follow-up, and often by needle biopsy of the liver, it was found that in general the plasma vitamin A levels were lowered in viral hepatitis, and not in obstructive jaundice. In hepatitis, a prompt fall in vitamin A levels occurred, with prompt return to normal coincident with clinical recovery. There was no quantitative relationship between vitamin A and bilirubin levels On the other hand, in obstructive jaundice the vitamin A levels remained normal for weeks or months In the small number with obstructive jaundice which did have low vitamin A levels, in five out of seven, metastases to the liver or extensive liver damage secondary to long-standing obstruction were proved at operation or necropsy.

In some cases in which parallel tests such as thymol turbidity, thymol flocculation, alkaline phosphatase, and urine urobilinogen were performed, the plasma vitamin A determination was found to point to the correct diagnosis when one or more of the other tests failed to do so The authors believed that plasma vitamin A levels constitute an additional useful test in the differential diagnosis of jaundice, pointing out that no single test is sufficient and that multiple procedures should always be employed

A significant clinical fact and one which has caused much misdirection

of effort is that normal pretreatment blood levels of vitamin A are found in many patients with hyperkeratosis syndromes, such as ichthyosis, Darier's disease, and pityriasis rubra pilaris; but in spite of this, improvement can be obtained in many of the cases by feeding vitamin A of animal or synthetic sources. Several explanations might be proposed, none of which is proven. It is theoretically possible that the individual with congenital disturbance of vitamin A metabolism produces a substance from carotenes which behaves chemically like vitamin A but does not have its biologic properties. Or it may be a vitamin A of quantitatively inferior biologic value or one which is not well utilized by the tissues. Another possible explanation is that these persons have elevated tissue thresholds, and in order to maintain epithelial integrity, higher than normal plasma and tissue levels are required. These speculations need investigation.

To add to the difficulties, response to vitamin A therapy in these syndromes is not uniform, and failures are frequently reported. Some of the failures may be due to ineffective preparations used in therapy, failure to recognize associated functional disorders in the gastrointestinal tract, hypothyroidism, or our present inability to determine other defects in the chain of vitamin A metabolism in a given patient.

Porphyria and photosensitive dermatoses.—The light-sensitive dermatoses are important and not adequately explained in most instances. One cause, the presence of abnormal porphyrins, is established, but accounts only for the relatively rare case seen in clinical practice. Porphyria is important since it may represent a prototype mechanism, and study of related metabolic abnormalities may elucidate other causes of photosensitivity. Brunsting has maintained a prolonged interest in this field, and in a recent publication, Brunsting & Mason (22) add three carefully studied cases to the literature. In each, the disease became manifest in adult life, and alcoholism and liver disease were probable precipitating factors. The cases were classified as the tardive phase of congenital porphyria with benign and chronic symptoms, although one of the patients presented clinical and laboratory features of acute porphyria. In this case, the patient's mother showed latent porphyria.

The skin in porphyria has a lowered threshold to injury by light and mechanical trauma which is manifested by the occurrence of erythema and blisters in exposed areas, increased melanin pigmentation, hypertrichosis, and milia formation. Although sunlight is known to elicit the skin lesions, attempts to reproduce lesions with artificial sources, such as ultraviolet and carbon-arc lamps, have not identified the spectral energies responsible. The extent of the cutaneous lesion may be proportional to the concentration of porphyrins in the tissues, the kind of porphyrin, the nature and concentration of the light source, and the factor of cumulative effect.

The syndrome known as acquired epidermolysis bullosa, which is clinically identical insofar as cutaneous findings and evidence of liver disease are concerned, is not accompanied by the presence of abnormal porphyrins.

This supports the thesis that the injured liver may put forth other abnormal metabolic products, as yet unidentified, which can produce photosensitization. Numerous cases of light sensitivity such as lupus erythematosus, urticaria and prurigo solare, solar eczematous dermatitis, hydroa aestivale and vacciniformis, and pellagra, which represent the bulk of photosensitive dermatoses in clinical practice, do not show abnormal porphyrins or demonstrable liver disease as such. That some unidentified and subtle metabolic disturbance is common to all of these is possible, but as yet purely hypothetical. Lamb and co-workers (23), reporting on 145 patients with solar dermatitis seen in the southwestern United States, found no evidence of disturbed porphyrin metabolism, and found that the activating wave lengths could not be identified.

Localized myxedema.—An excellent discussion of localized myxedema and its association with progressive exophthalmos is presented by Curtis and co-workers (24), and includes case reports and a thorough survey of the mechanism of production of the two lesions The thesis is put forward that the two conditions are allied manifestations of the same underlying disorder, both being due to excess of pituitary thyrotropic hormone. The phenomenon occurs most often following surgical or "chemical" thyroidectomy in diffuse toxic goiter and presumably is due to absence of effective inhibitors of thyrotropic hormone, namely, thyroid cells and/or thyroid secretion Although thyroid extract can be shown to effectively depress the activity of thyroid-stimulating hormone in the rat, the administration of thyroid to patients with localized myxedema and progressive exophthalmos is of little value. The authors do not discuss this contradiction.

Acne vulgaris.—Because of its great prevalence and the major physical and physic damage it so often produces, acne vulgaris represents a dermatologic and medical problem of the first rank. The past several years have seen the beginning of a new and productive era in the study and treatment of this disease, pertinent and crucial facts have been established in etiology, and rational and potent medical measures are available for treatment. The numberless traditional, useless, and often harmful methods which have accumulated over the years can now be discarded.

Although there have been many important contributors, the names of Hamilton (25), Lawrence & Werthessen (26), and Barber (27) are outstanding. The last has presented a masterful exposition of the newer concepts regarding the role of sex hormones, and the reference cited is recommended to all readers for careful study. A brief summary of Barber's essay follows: (*a*) The essential and primary lesion of acne is the comedone. (*b*) Comedones develop *pari passu* with pubic and axillary hair, which both in the male and female are known to depend upon stimulation of the pilosebaceous system by androgens; thus, comedone formation is analogous to development of sexual hair. (*c*) Androgens are known to induce hyperkeratosis especially of the pliosebaceous orifices, which lesion is the initial stage in the development

of the comedone. (*d*) Without androgenic stimulation of pilosebaceous follicules, acne does not occur. (*e*) The determining factors are two—first, a relative excess of androgens, and second, a susceptibility of the receptor mechanism—the pilosebaceous apparatus. (*f*) The development of the inflammatory phases of acne depends upon other factors, including especially bacterial activity and metabolic influence, particularly carbohydrate metabolism and hydration of the skin. (*g*) Adequate doses of estrogens will "cure" acne vulgaris

The elucidation of the role of sex hormones has opened a fundamental approach to the problem and to the primary lesion—the comedone. Additional factors which must be considered in individual cases are hypothyroidism, which appears to have a high incidence (even though transient) in puberty and the immediate prepubertal years; disturbed vitamin A metabolism, anemia, physical fatigue; and emotional stresses. All of these are now better understood. In addition, the antibiotics, especially aureomycin, are available for the control of the severe suppurative components in some cases

It is no longer necessary to experiment with the patient's diet. A high-protein, low-carbohydrate diet is satisfactory, and the only specific foods which seem to aggravate the condition in some individuals are chocolate, nuts, and butter fat (in the rare case)

There is a healthy and increasing trend to decrease or completely eliminate the use of roentgen rays in the treatment of acne. An outstanding expert in the field of radiotherapy in the skin, Andrews (28), has well stated this position: "I have not used roentgen radiation in the treatment of acne in well over a year. The results appear to be much better than with roentgen therapy and the old routine therapy. I doubt that I shall ever use roentgen irradiation to treat acne again " (The reviewers have not used x-ray in the treatment of acne in their own practice for several years and are completely convinced that the results are as good if not better than with the use of x-ray.)

Advances have also been made in local medications utilizing sulfur in newer penetrant vehicles. Outstanding among these is "intraderm sulfur," as developed and reported by MacKee and co-workers (29).

That estrogenic substances can control acne seems well established However, optimum dosage and timing in relation to the menstrual period in the female have not as yet been determined. There is still much disagreement on the possible parallel effects on other organs and systems which may be deleterious in both sexes It is also possible that progestins may be of value, with possibly fewer disadvantages [Way & Andrews (28)] The promise is so great and the basis of the therapy so well established that every effort should be made to develop an optimum treatment schedule. Our own experience indicates that small doses of estrogens in the physiological range over a period of several months are adequate in mild and moderately severe cases. In general, the dosage levels used in this country have been much smaller than those employed by Barber and the British dermatologists.

Hair Growth and Hair Loss

Hirsutism.—Discussing essential hirsutism, i.e., hypertrichosis without demonstrable associated endocrine disturbance, Callaway and co-workers (30) reviewed current evidence on normal and abnormal hair growth. Hirsutism represents a major psychological problem in the female, and misconception is widespread among physicians relative to the role of endocrines in control of hair growth. Danforth (31) stated that although humoral control of hair growth probably exists, not all hair follicles are affected. Danforth classified hair as (*a*) general body hair (lanugo), (*b*) ambosexual hair of males and females, pubic and axillary, stimulated by hormones and equivalent in both sexes, (*c*) truly sexual hair, the beard in males, and to a lesser extent the terminal hair of shoulders, anterior chest, and abdomen. Hamilton (32) stated that (coarse) terminal hair on the external ear is absolutely characteristic of the male.

Endocrine glands concerned with hair growth are adrenal cortex, gonads, thyroid, and anterior pituitary. Danforth stated that general body hair is not influenced by endocrine factors Ambosexual hair can be stimulated by adrenal cortex in the absence of gonads. Truly sexual hair in males is dependent upon gonadal androgens.

Hirsutism has been reported in encephalitis, neuritis, mumps, gonadal teratoma, mental retardation, and multiple sclerosis. Endocrine diseases associated with hirsutism are basophilic tumors or hyperplasia of the pituitary, neoplasms or hyperplasia of the adrenal cortex, arrhenoblastoma and adrenal rest tumors of the ovary, tumors of the thymus with secondary adrenal hyperplasia, and luteomas

Callaway and co-workers (30) contrasted a group of women with "essential" hirsutism with a group with known endocrine disorders, the patients being selected for comparable clinical and laboratory data Their conclusions are clear-cut and significant. The intensity, amount, and distribution of hirsutism are not diagnostic evidence of endocrinopathy. Patients with established endocrine disorder may not show major hirsutism Proof of normal ovulatory function rules out virilizational syndromes. Amenorrhea longer than 12 months associated with hirsutism is of grave significance "The chief basis of the differentiation of essential hirsutism and hirsutism associated with endocrine disease lies in the clinical approach rather than in laboratory investigation." There is no evidence that endocrine therapy will favorably influence essential hirsutism Excessive hair falls slowly if at all. Even in virilizing syndromes after correction, hirsutism is one of the most persistent and slowly reversible of all signs and symptoms. The authors deprecate the use of estrogens in treatment of hirsutism in women with normal ovarian function, since no benefit can be expected, and possible untoward effects are considerable

Premature baldness—A thought-provoking and convincing theory of the pathogenesis of ordinary human baldness is presented by Szasz & Robertson (33), integrating well-established concepts of previous workers with ob-

of the comedone (*d*) Without androgenic stimulation of pilosebaceous follicules, acne does not occur. (*e*) The determining factors are two—first, a *relative excess of androgens,* and second, *a susceptibility of the receptor* mechanism—the pilosebaceous apparatus. (*f*) The development of the inflammatory phases of acne depends upon other factors, including especially bacterial activity and metabolic influence, particularly carbohydrate metabolism and hydration of the skin (*g*) Adequate doses of estrogens will "cure" acne vulgaris

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There is a healthy and increasing trend to decrease or completely eliminate *the use of roentgen rays in the treatment of acne. An outstanding* expert in the field of radiotherapy in the skin, Andrews (28), has well stated this position "I have not used roentgen radiation in the treatment of acne in well over a year. The results appear to be much better than with roentgen therapy and the old routine therapy. I doubt that I shall ever use roentgen irradiation to treat acne again " (The reviewers have not used x-ray in the treatment of acne in their own practice for several years and are completely convinced that the results are as good if not better than with the use of x-ray.)

Advances have also been made in local medications utilizing sulfur in newer penetrant vehicles Outstanding among these is "intraderm sulfur," as developed and reported by MacKee and co-workers (29).

That estrogenic substances can control acne seems well established. However, optimum dosage and timing in relation to the menstrual period in the female have not as yet been determined There is still much disagreement on the possible parallel effects on other organs and systems which may be deleterious in both sexes. It is also possible that progestins may be of value, with possibly fewer disadvantages [Way & Andrews (28)] The promise is so great and the basis of the therapy so well established that every effort should be made to develop an optimum treatment schedule Our own experience indicates that small doses of estrogens in the physiological range over a period of several months are adequate in mild and moderately severe cases. In general, the dosage levels used in this country have been much smaller than those employed by Barber and the British dermatologists.

Hair Growth and Hair Loss

Hirsutism.—Discussing essential hirsutism, i.e., hypertrichosis without demonstrable associated endocrine disturbance, Callaway and co-workers (30) reviewed current evidence on normal and abnormal hair growth. Hirsutism represents a major psychological problem in the female, and misconception is widespread among physicians relative to the role of endocrines in control of hair growth. Danforth (31) stated that although humoral control of hair growth probably exists, not all hair follicles are affected. Danforth classified hair as (*a*) general body hair (lanugo), (*b*) ambosexual hair of males and females, pubic and axillary, stimulated by hormones and equivalent in both sexes, (*c*) truly sexual hair, the beard in males, and to a lesser extent the terminal hair of shoulders, anterior chest, and abdomen. Hamilton (32) stated that (coarse) terminal hair on the external ear is absolutely characteristic of the male.

Endocrine glands concerned with hair growth are adrenal cortex, gonads, thyroid, and anterior pituitary. Danforth stated that general body hair is not influenced by endocrine factors. Ambosexual hair can be stimulated by adrenal cortex in the absence of gonads. Truly sexual hair in males is dependent upon gonadal androgens.

Hirsutism has been reported in encephalitis, neuritis, mumps, gonadal teratoma, mental retardation, and multiple sclerosis. Endocrine diseases associated with hirsutism are basophilic tumors or hyperplasia of the pituitary, neoplasms or hyperplasia of the adrenal cortex, arrhenoblastoma and adrenal rest tumors of the ovary, tumors of the thymus with secondary adrenal hyperplasia, and luteomas.

Callaway and co-workers (30) contrasted a group of women with "essential" hirsutism with a group with known endocrine disorders, the patients being selected for comparable clinical and laboratory data. Their conclusions are clear-cut and significant. The intensity, amount, and distribution of hirsutism are not diagnostic evidence of endocrinopathy. Patients with established endocrine disorder may not show major hirsutism. Proof of normal ovulatory function rules out virilizational syndromes. Amenorrhea longer than 12 months associated with hirsutism is of grave significance. "The chief basis of the differentiation of essential hirsutism and hirsutism associated with endocrine disease lies in the clinical approach rather than in laboratory investigation." There is no evidence that endocrine therapy will favorably influence essential hirsutism. Excessive hair falls slowly if at all. Even in virilizing syndromes after correction, hirsutism is one of the most persistent and slowly reversible of all signs and symptoms. The authors deprecate the use of estrogens in treatment of hirsutism in women with normal ovarian function, since no benefit can be expected, and possible untoward effects are considerable.

Premature baldness.—A thought-provoking and convincing theory of the pathogenesis of ordinary human baldness is presented by Szasz & Robertson (33), integrating well-established concepts of previous workers with ob-

servations of their own. The argument, briefly, is as follows: Given the average male with the genetic background which determines the requisite skull shape and with adequate levels of testosterone which reduce the thickness of the fat pad in the central portion of the scalp, the stage is then set for the action of shearing stresses in the dermis of the scalp which over a long period of time interfere with the circulation to the scalp in this area. The argument to this point is well documented by the work of previous observers. Szasz & Robertson believe on the basis of their own observations that the characteristic facial expression of the man who is to become bald is *essentially one of tension, and as can be shown on an anatomical basis*, tension of facial muscles is accompanied by tension of the scalp muscles, which is the immediate cause of the shearing stresses in the scalp. Their argument is presented in logical and convincing terms

Limitations of Roentgen Therapy

A most significant paper on the limitations and contraindications to the use of roentgen therapy in cutaneous diseases by Lane (34) is heartily recommended for careful reading. Many, including the reviewers, have been alarmed by the ever-increasing and often indiscriminate use of roentgen rays in the treatment of skin diseases, both by dermatologists and others. Much is said about the value of roentgen rays, too little about the limitations and hazards Lane lists as primary or absolute contraindications: (*a*) improper standardization of equipment, (*b*) inadequate training of personnel, (*c*) undetermined amount of previous radiation, (*d*) diseases characterized by atrophy and scarring, (*e*) blood dyscrasias, and (*f*) diseases known not to respond to radiation. Partial contraindications are: (*a*) lack of a definite diagnosis, (*b*) failure to respond after a fair trial, (*c*) acute inflammatory processes, and (*d*) diseases of the scalp other than certain types of fungus infection.

The most common abuses in the reviewers' experience have been radiation in conditions in which no benefit can be expected, radiation in cases in which no diagnosis has been established, and the complete lack of any idea as to what constitutes a fair trial, since little or no controlled data are available on how much x-ray is needed to produce a response in any given condition (other than malignancy and keloid).

Bacterial Diseases

The treatment of certain bacterial diseases, primary and secondary, has been revolutionized by the introduction of the newer antibiotics The diseases under consideration constitute the largest numerical group of skin disorders, when the secondary pyogenic complications of acute and chronic eczematous dermatoses are included Furthermore, it has been the secondary infection and its consequences which have accounted for the long duration of many primarily nonbacterial dermatoses The primary bacterial diseases include impetigo, ecthyma, furunculosis and carbuncle, suppurative fol-

liculitis including the notoriously resistant sycosis barbae, pustular eruptions of the hands and feet, dermatitis repens, many intertrigos and localized cellulitis secondary to fissures, many cases of otitis externa, pemphigus neonatorum, infectious eczematoid dermatitis, erysipelas and erysipeloid, many chronic ulcers following trauma, and others. Secondary infection with the development of sensitization dermatitis and dissemination may occur in any acute dermatitis such as contact dermatitis from chemicals and plants and any chronic pruritic dermatosis such as neurodermatitis At times, the infection component dominates the clinical picture, and cure depends upon its control Prior to the effective antibiotics, control was well nigh impossible. Except for the simple, uncomplicated infections such as impetigo, both systemic and local treatment are necessary. Penicillin, aureomycin, and terramycin systemically have been outstandingly effective against the bacteria commonly present.

Bacitracin is by far the most desirable agent for local use (35), having high bactericidal power, a broad spectrum, and extremely low sensitizing index. All previously used agents such as sulfonamides, mercurials, penicillin, streptomycin, nitrofurazone and others, although of moderate value in killing bacteria, caused so much local irritation, and, more important, skin sensitization with immediate or delayed disseminated sensitization dermatitis that often the treatment was worse than the disease. Sensitization with bacitracin even after very prolonged use is uncommon, most reports indicating it to be less than half of one per cent

Bacitracin is moderately effective in commercial ointments which utilize petrolatum-lanolin bases and which are stable without refrigeration for at least one year We have found that the drug is even more effective when freshly prepared in a water-miscible base, 500 units per gm. of ointment. This preparation must be refrigerated and material loss of potency occurs after 7 to 10 days as occurs, also, in aqueous solutions of the drug

Aureomycin has been outstandingly effective in the treatment of staphyloccocal infections heretofore very resistant to treatment, many of which did not respond to penicillin. Terramycin may be equally valuable, but experience thus far is limited These drugs are used in doses of 1 to 1 5 gm. daily for 5 to 7 days Response is usually apparent in the average case in this period. However, longer periods of treatment may be required, or the course repeated Optimum dosage and period of treatment are not fully established

Other Recent Developments

Psoriasis—Psoriasis continues to be an enigma Numerous effective treatments are reported, but a carefully controlled large series of cases is yet unavailable. The difficulty probably lies in the fact that psoriasis is a reaction pattern induced by several precipitating factors which vary in different individuals A single pathogenetic mechanism and a single cure is not to be expected That psoriasis is an internal systemic disturbance seems well established.

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treatment period from 2 to 6 weeks No specific advantage was noted in this form of treatment.

Calciferol—Pariser & Anderson (42) add three more cases of lupus vulgaris in which large doses of vitamin D_2 (calciferol) caused involution of the skin lesions A brief review of the recent literature is presented. Appropriate warning is given concerning the potential hazards of the treatment. In this connection, it seems necessary to point out that calciferol therapy has been somewhat abused in dermatologic therapy. Calciferol has its optimum effect in lupus vulgaris, a serious and mutilating disease, and the use of therapy which carries considerable hazard is justified. However, calciferol has been used in relatively benign disorders, such as "rosacea-like" tuberculid, acne scrofulusorum, and granuloma annulare, the tuberculous etiology of which is very doubtful and in which the calciferol treatment is more dangerous than the disease As pointed out by Bradley (48), numerous reports in recent years indicate that nephrocalcinosis, renal insufficiency, and widespread calcification of tissue may follow the intake of 100,000 I.U. of vitamin D per day for extended periods.

ACTH and Cortisone

Because of the widespread interest and potential significance of ACTH and cortisone, we believe it desirable to include the following comments and survey, even though isolated case reports, personal experience, and communication with those who have used these agents in the treatment of several skin disorders constitute the only available material for review. The reviewers' appraisal of the results to date agrees well with the statement of O'Leary (43), reporting the experience at the Mayo Clinic, that these hormones in the treatment of skin diseases to date are "popular, but I fear disappointing" Unfortunately, the literature as yet contains very few detailed case reports in which favorable results have been maintained over critical periods of time The experience of many observers, as yet unpublished, does not substantiate the optimistic outlook of the early general statements released in the medical and lay press and by the drug manufacturers. On the other hand, profound changes are unquestionably produced in many different and completely unrelated inflammatory skin disorders, and the possible usefulness of this action is yet to be determined

ACTH and cortisone have been used in the following skin disorders with variable and inconsistent results. acute and subacute disseminate lupus erythematosus, scleroderma, periarteritis nodosa, dermatomyositis, psoriasis, pemphigus, eczema of various types including generalized neurodermatitis, and chronic urticaria. These diseases are characterized by erratic and unpredictable clinical courses, spontaneous remission of variable duration, and in some instances, remissions of variable duration induced by a number of therapeutic agents which later fail when applied in the same cases in a later period of activity. It is, therefore, extremely difficult to evaluate any form of

Since psoriasis has been reported to respond to ACTH and cortisone, the report of Reiss (36) is of interest. In a study of 25 cases, he found the plasma cholesterol to average 263 mg. per cent with 5 cases over 300 mg. He observed diminished urinary ketosteroids in 12 cases, flat glucose tolerance curve in 9 cases, and vitamin C depletion (using saturation test) in 22 cases He noted that psoriasis usually improves in pregnancy and jaundice and suggested that parakeratosis may represent a relatively specific response to adrenal hypofunction.

The use of undecylenic acid orally administered caused widespread interest in the past year following a very enthusiastic and unfortunately premature and "uncontrolled" publication. It has not proven to be of value.

Since psoriasis runs a capricious course and many measures seem to be effective temporarily, the evaluation of any new treatment must be done with scrupulous care. The list of psoriasis "cures" is endless, and to date not one is consistently good

Pemphigus.—Initial reports and unpublished data from numerous sources indicate that ACTH and cortisone (see below) exert a profound effect in the treatment of pemphigus It is, therefore, of interest to recall the writings of the past 10 years, especially those of Talbott & Coombs (37) which presented evidence that at least in some cases of pemphigus, significant disturbance of electrolyte balance can be demonstrated and of Goldzieher (38) relative to adrenal cortical injury. It would appear that some of the pieces of the pemphigus puzzle are beginning to fall into place, and on a rational basis.

Hunt & Minot (39) investigated the possible relationship of hyaluronidase and the phenomenon of bulla formation in pemphigus. In pemphigus patients, they found no evidence of increased hyaluronidase in the skin, serum or bulla fluid, nor decreased hyaluronic acid in the skin, as compared to normals

Disseminated lupus erythematosus—Montgomery & McCreight (40) studied 286 cases of disseminated lupus erythematosus seen up to 1948 at the Mayo Clinic. They conclude that the "L E cell" is of diagnostic and prognostic value in disseminated lupus erythematosus with and without skin lesions, histologic changes in the skin do not support the concept that this is primarily a collagenous disease; the cause is unknown They briefly mentioned the very vital question of differentiating solar dermatitis from lupus erythematosus, a subject worthy of a major publication (It is the experience of the reviewers that dermatologists too often make a diagnosis of lupus erythematosus without critical judgment in patients with photosensitive dermatoses of the face This causes unnecessary alarm for the patient, to say nothing of adulterating the data on therapeutic results)

Chloramphenicol—Beinhauer (41) treated 76 cases of skin diseases of established or suspected virus etiology, including erythema multiforme, herpes zoster, herpes simplex, verrucae, molluscum contagiosum, varicella, and dermatitis herpetiformis Daily dosage ranged from 500 to 2,000 mg.

we believe that it is representative of the general experience. These compounds appear to have the capacity to block tissue responses to toxins and antigens in the skin as well as in other organs and systems in a nonspecific fashion, and there is no evidence that the fundamental etiologic, pathogentic mechanisms are affected. With the possible exception of pemphigus, there is no evidence that there is any deficiency of adrenal function in the diseases here discussed. It appears that the drugs as presently constituted are not suitable for the treatment of chronic diseases of unknown cause, but it may be reasoned that the drugs could be useful in certain acute dermatoses to block the destructive tissue responses to temporarily acting toxic or noxious agents, for example, in allergic states and drug reactions. Experience in this direction may be forthcoming as the available supplies of the drugs increase and are diverted from those conditions in which they are now known to be of little value. An obvious merit of their use in acute conditions of relatively short duration is that the major physiologic disturbance attending their prolonged use can be avoided

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treatment without relatively large numbers of cases carefully classified and observed over long periods of time.

Disseminated lupus erythematosus.—O'Leary (43), reporting on three cases treated with cortisone, stated that there was remarkable remission in the clinical signs and symptoms, such as cutaneous inflammation, fever, arthralgia, and general toxicity, whereas the laboratory findings changed relatively little. On discontinuation of the drug, "L. E. cells" could be found consistently and clinical relapse was prompt. Remission was induced by retreatment on two subsequent occasions, but the patients eventually died, severe psychic disturbances having occurred some time during the course of treatment in two of these cases.

This report is generally consistent with those from other sources and with the experience on the dermatology and medical services of the Los Angeles County Hospital in using ACTH Possibly the most comprehensive published report to date is that of Baehr & Soffer (44), who found that although remissions could be induced, no permanent results were obtained.

Scleroderma.—In two cases discussed by O'Leary (43), each of which received three courses of cortisone, the initial response was more dramatic than in any other condition treated, but unfortunately relapse was equally prompt when treatment was discontinued.

Dermatomyositis—O'Leary (43) reported a case of acute dermatomyositis treated with cortisone in which there was marked remission of the inflammatory changes but in which the muscular weakness was progressive and in which the patient died six weeks after the treatment was begun. Oppel and co-workers (45) report an extended remission in a case of chronic dermatomyositis treated with ACTH.

Pemphigus—In cases of acute exfoliative pemphigus and acute pemphigus vulgaris treated with cortisone, O'Leary (43) reported that both patients died, in spite of initial response to treatment, and the exfoliative case relapsed under treatment during the third course. A case of pemphigus vegetans presented before the Los Angeles Dermatological Society by Newman (46) has maintained satisfactory remission for four months (at the time of this writing) after treatment with ACTH.

Eczema.—We have observed several cases of exudative neurodermatitis which had failed to respond to a great variety of therapeutic agents over a period of several years, which responded promptly to cortisone or ACTH. One case treated with a total of 1,200 mg of cortisone had prompt response and has maintained remission for two months Sternberg (47) reports that cortisone has little value in neurodermatitis, pemphigus, lupus erythematosus, and although initial response can be obtained with ACTH, relapse is prompt upon discontinuance of the drug, and no satisfactory maintenance dose could be established On the other hand, we have seen several instances of exudative eczematous dermatitis which showed no response to the initial course of ACTH

Discussion.—Although our survey of this subject is obviously incomplete,

THE GENERAL-ADAPTATION-SYNDROME

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With the concept of the general-adaptation-syndrome (G-A-S), we have attempted to integrate a number of seemingly quite unrelated observations into a single unified biologic system. The literature concerning this field has become so voluminous that it would be impossible to survey it within the frame of this brief synopsis Since, on the other hand, it would be unadvisable and misleading to select a few references at random for discussion here, the reader is referred to the bibliography given in our recent monograph concerning this subject (1) upon which the present review is based. Some of the more recent references by the author which may be accessible to many physicians are listed at the end of the chapter.

By way of an historic introduction, one might mention, among the many earlier observations pertaining to this general field, the work of Claude Bernard, who showed how important it is to maintain the constancy of the "milieu intérieur," Cannon's concept of "homeostasis," Frank Hartmann's "general tissue hormone" theory of the corticoids, Dustin's observations on the "caryoclastic poisons," the "post-operative disease," the curative action of fever, foreign proteins, and of other "non-specific therapeutic agents," the "nephrotoxic sera" of Masugi and the "Goldblatt clamp" for the production of experimental renal hypertension.

At first sight, it would seem that all these observations have little in common and that there is no reason to attempt their integration into a unified system of physiologic and pathologic events Yet, the above-mentioned monograph (1)—and indeed most of the author's research work—has been devoted to the construction of bridges between these and many additional facts since they were thought to be interconnected in nature. Through the comprehension of their unity, we hoped to learn how to use them better for the understanding of life and the treatment of disease. The keynote of this unification was the tenet that all living organisms can respond to stress as such and that, in this respect, the basic reaction pattern is always the same irrespective of the agent used to produce stress We called this response the General-Adaptation-Syndrome (G-A-S), and its derailments, the Diseases of Adaptation

Anything that causes stress endangers life unless it is met by adequate adaptive responses, conversely, anything that endangers life causes stress and adaptive responses Adaptability and resistance to stress are fundamental prerequisites for life and every vital organ and function participates in them In order to present a well-proportioned outline of the G-A-S, it is necessary, therefore, to peruse every branch of physiology, biochemistry, pathologic

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pressure represent the interplay between a force and the resistance offered to it.

In addition to damage and defense, every stressor also produces certain specific actions, e.g., anesthetics act upon the nervous system, diuretics upon water metabolism, insulin upon the blood-sugar, quite apart from their stressor effects. Hence, the G-A-S never occurs in its pure form, but is always complicated by superimposed specific actions of the eliciting stressors. In contemplating any biologic response, e g , a spontaneous disease, an intoxication, a psychosomatic reaction, it is usually quite difficult to identify individual manifestations as being due respectively to damage, defense, or specific actions of the provocative agent. Only nonspecific damage and defense are integral parts of the G-A-S, but the specific actions of the eliciting stressors modify the course of the resulting G-A-S, e.g., the glycemic curve will deviate from the characteristic pattern if insulin is used as the stressor agent; the neurologic manifestations will be atypical if the G-A-S is provoked by ether. In this sense, they act as conditioning factors Certain circumstances, not directly related to the stress situation, are also prone to alter the course of the G-A-S. Among these, heredity, pre-existent disease of certain organ systems, and the diet are especially important

The schematic drawing (p. 330) disregards the specific actions of stressors, since they are not part of the G-A-S. It attempts to depict only the main pathways through which nonspecific stress itself affects the organism and the manner in which such reactions are conditioned.

Defense

The systemic defense measures against both general and localized (topical) injuries are coordinated through the hypothalamic vegetative centers and the hypophysis. The intitial pathways through which stressors act upon these centers are not yet known Probably, either humoral or nervous impulses coming from the site of direct injury can induce the hypothalamus-hypophysis system to gear the body for defense Subsequently both of the two great integrating mechanisms, the nervous and the endocrine system, are alerted

The nervous defense mechanism.—Nervous impulses descend from the hypothalamic vegetative centers, through the autonomic nerves, to the peripheral organs The splanchnics induce the adrenal medulla to discharge adrenergic hormones (epinephrine and norepinephrine) into the blood. Other adrenergic nerves influence their target organs directly through fibers which, in the final analysis, again act through the liberation of adrenergic compounds, in this case at their endings in the effector organs themselves (blood vessels, glands, etc.). Presumably, the discharge of adrenergic hormones into the circulation is most effective when they are needed throughout the body, while the sympathetic nerves are better suited to impart similar impulses selectively to certain circumscribed territories. The most conspicuous results of such neuro-humoral discharges are changes in the contractility of

anatomy, and clinical medicine in search of the "stress factor" in all aspects of normal and abnormal life.

Unfortunately, during the past few years there existed a tendency to apply to clinical medicine certain aspects of this problem in a rather haphazard manner without much effort to understand the underlying physiologic mechanisms. Since some of the hormones produced during stress have definitely toxic effects, this kind of procedure is not without danger. It appears desirable at this time, therefore, to survey at least the main lines of the G-A-S.

It will take many years, indeed many generations, before the details of the G-A-S are satisfactorily elucidated In fact, we shall never truly understand this phenomenon since the complete comprehension of life is beyond the limits of the human mind. But there are many degrees of elucidation It seems that now the fog has been just sufficiently dispersed to perceive the G-A-S through that measure of "twilight" which permits us to discern the grandeur of its outlines but fills us with the insatiable desire to see more.

We realize that many lines in our sketch will have to be hesitant, some even incorrect, if we try to put on paper now what we still see only vaguely. But a preliminary map—albeit largely incomplete and partly inaccurate—is needed now by those eager to exploit this field which holds so much promise for all who suffer from stress! We hope that these pioneers in uncharted territories will accept my partial and distorted map in the spirit in which it is offered, to complete and rectify it. It is in this sense that I should like the reader to consider the following synopsis of what I think I see.

Principal Facts and Theories upon Which the G-A-S Concept Is Based

Apart from the many specific defense reactions (e g., formation of specific antibodies, adaptation to cold, habituation to morphine, hypertrophy of much-used muscle groups), there is an integrated syndrome of closely interrelated adaptive reactions to nonspecific stress itself; this has been termed the "General-Adaptation-Syndrome." It develops in three stages: the Alarm-Reaction, the Stage of Resistance, and the Stage of Exhaustion Most of the characteristic manifestations of the Alarm-Reaction (tissue catabolism, hypoglycemia, gastrointestinal erosions, discharge of secretory granules from the adrenal cortex, hemo-concentration, etc) disappear or are actually reversed during the Stage of Resistance, but reappear in the Stage of Exhaustion. This suggests that the ability of living organisms to adapt themselves to changes in their surroundings, their adaptability or "adaptation energy," is a finite quantity; its magnitude appears to depend largely upon genetic factors

In the G-A-S, the manifestations of passive, nonspecific damage are intricately intermixed with those of active defense. This is an inherent characteristic of the stress, which elicits the G-A-S. In the biologic sense, stress is the interaction between damage and defense, just as in physics, tension or

eral resistance in the cardiovascular system, and hence, the blood pressure rises (cf. below)

There is some evidence of a simultaneous cholinergic discharge during systemic stress Concurrent activation of both agonists and antagonists occurs in many effector systems during the G-A-S. Presumably, it helps to stabilize the target organs in the face of very powerful stimuli which might otherwise cause excessive deviations from the norm. This concurrent tension of agonists and antagonists is somewhat reminiscent of the simultaneous contraction of flexor and extensor muscles, for instance in a limb, to prepare against possible displacement by a blow which may come from any direction However, damage (shock) endangers life particularly through vasodepressor and hypotensive actions; hence, the predominant response during the G-A-S is a defensive (prophylactic) vasoconstriction and hypertension.

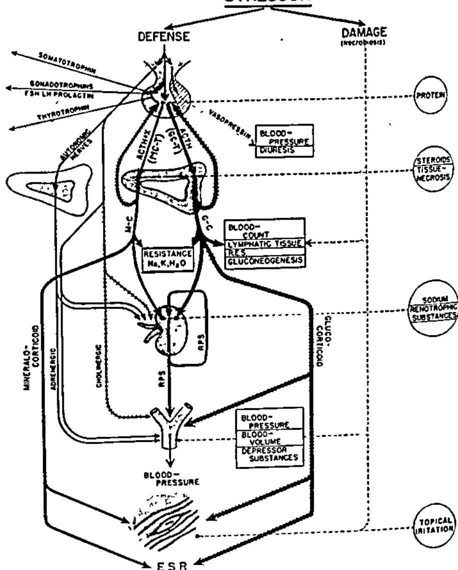
The nervous system also participates in many other defensive reactions during the G-A-S, e g , the regulation of water metabolism through the hypophyseal stalk and posterior lobe, the blood sugar through the hepatic branches of the sympathetic division, and the blood count through splenic contraction, but for the sake of simplicity, these are not specifically indicated in our schematic drawing.

The hormonal defense mechanism.—The principal endocrine response to stress is characterized by the so-called "shift in anterior lobe hormone production." This consists in a diminished secretion of somatotrophin, the gonadotrophins (follicle stimulating hormone, luteinizing hormone, prolactin) and thyrotrophin—which are not essential for the maintenance of life during conditions of emergency—accompanied by an increase in the secretion of adrenocorticotrophic hormone (ACTH) Apparently, the anterior lobe is unable to produce all its hormones at an optimal rate it if is called upon to discharge extraordinarily large amounts of corticotrophin.

ACTH is a glucocorticotrophic hormone It induces the adrenal cortex to produce predominantly glucocorticoids, e.g , compound F, cortisone. The latter act upon the blood count (lymphopenia, eosinopenia, polymorphonuclear leucocytosis), the thymicolymphatic tissue (lympholysis), the reticuloendothelial system (increased phagocytosis and antibody formation), and gluconeogenesis (transformation of nonsugars into carbohydrates). The glucocorticoids presumably influence resistance in many additional ways which have not yet been fully analyzed. Through all these actions, such steroids help to maintain adrenalectomized animals, even during exposure to stress

All glucocorticoids so far examined possess some mineralocorticoid activity (actions upon sodium, chlorine, potassium, and water metabolism), thus, they resemble the pure mineralocorticoids, but the latter are much more potent in this respect and possess no glucocorticoid action Hence, changes in mineral and water metabolism observed after the injection of ACTH do not necessarily reflect the production of pure mineralocorticoids by the adrenal.

The action of glucocorticoids upon the kidney has not yet been exten-



smooth muscle Due to an adrenergic vasoconstriction, peripheral resistance increases and the blood pressure rises. This hypertensive response may be further accentuated by an increased cardiac volume and the opening of the renal shunt, which deviates blood from the cortical glomeruli to the juxtamedullary region of the kidney This neurogenic activation of the shunt is -ite comparable to that induced by mechanical interference with the ar- ... into the kid-

simultaneously with the inhibition of glomerular filtration, increases the endocrine activity of the nephron. At the same time, the inactivation of renal pressor substances is impeded and a hormonally induced renal hypertension ensues.

Presumably, both stimulation of renal pressor substances formation and inhibition of their destruction is thus induced by mineralocorticoids. This affects the blood vessels. At first, the resulting excess of renal pressor substances causes a functional vasoconstriction with an increase in peripheral resistance and blood pressure. More prolonged overdosage with mineralocorticoids results in arteriosclerotic changes (especially periarteritis nodosa and hyalinosis) with a consequent permanent increase in peripheral resistance and blood pressure.

In this respect, mineralocorticoids and glucocorticoids mutually antagonize each other, but since, at least at certain dose levels, their actions upon the kidney are synergistic, it depends upon the conditioning circumstances whether the administration of glucocorticoids to animals overdosed with mineralocorticoids increases or decreases the blood pressure (cf. also conditioning effect of sodium and renotrophic substances, below).

There is no definite evidence to prove that either type of corticoid has any direct vasopressor effect. Addition of corticoids to perfused vessel preparations does not cause them to contract. Nevertheless, mineralocorticoids can augment the blood pressure even in the absence of the kidney, presumably by raising the blood volume through their effect on mineral and water metabolism.

Both types of corticoids act back upon the anterior lobe and inhibit its ACTH production through the so-called phenomenon of "compensatory atrophy." It is not yet known whether corticoids also impede the endogenous production of that "X factor" which renders ACTH mineralocorticotrophic. However, this is very probable, since otherwise ACTH therapy would only aggravate conditions characterized by symptoms of mineralocorticoid overdosage. If the production of the "X factor" is inhibited in the same manner as that of ordinary ACTH, then the therapeutic action of ACTH is readily explicable In both instances, the pituitary is exposed to an excess of glucocorticoids. The latter are even more potent in eliciting the compensatory atrophy phenomenon than the mineralocorticoids Consequently, endogenous corticotrophic stimuli (including "X factor") are virtually eliminated and the exogenously administered, predominantly glucocorticotrophic ACTH acts uninfluenced upon the adrenal cortex.

There is much to suggest that at least certain types of stress, e.g, emotional stimuli, can increase the production of antidiuretic hormone, which is probably identical with vasopressin. This effect is undoubtedly mediated by nerve tracts descending from the hypothalamus to the posterior lobe since, unlike the discharge of ACTH, it is abolished by transection of the hypophyseal stalk Vasopressin exerts important effects upon the blood pressure and diuresis, these may be superimposed upon the typical reaction pattern during the G-A-S However, the rôle of vasopressin secretion during systemic stress has not yet been adequately investigated.

sively studied. However, preliminary investigations show that they cause marked hyperemia of the glomeruli and may render the latter permeable to proteins and even blood. Heavy overdosage with glucocorticoids can produce severe hyalinization and disintegration of glomeruli. This is followed by a rise in blood pressure, presumably mediated through the *renal pressor substances system*. *In this* respect, glucocorticoids and mineralocorticoids may *mutually* synergize each other.

The glucocorticoids inhibit the production of arteriosclerotic changes (especially periarteritis and hyalinosis) In this respect, they antagonize the effects of mineralocorticoids. The glucocorticoids generally inhibit excessive proliferation of fibrous tissue, the formation of *intercellular protein deposits* (e g., hyalinosis, collagen disease, allergies), and excessive granulomatous defense reactions against those local irritants which stimulate fibroplastic inflammatory reactions in mesenchymal tissue. They also tend to decrease the erythrocyte sedimentation rate through their effect upon the blood proteins. In all these respects, they act as antagonists of the *mineralocorticoids*. The mechanism of the marked anti-allergic and antihistaminergic actions of glucocorticoids has not yet been elucidated. It may depend upon the breakdown of the proteins which store histamine as a protein-histamine complex

Many data suggest that under conditions of stress, mineralocorticoid production is likewise increased. Such a rise can also be elicited by certain *impure*, mineralocorticotrophic, anterior pituitary extracts, for instance *lyophilized anterior pituitary tissue* (LAP). Threshold doses of LAP are further activated in this respect by simultaneous administration of ACTH. Apparently the action of the latter can be qualitatively altered by some factor ("X") present in crude pituitary extracts and LAP. This "X factor" appears to be a specific pituitary principle, as it has not been found to occur in similar preparations of other tissues (e.g , liver). The "X factor" is manifestly not ACTH, but it may be identical with one of the other, already known, hypophyseal hormones. It could also be a special hypophyseal principle, not hitherto identified Be this as it may, it has now definitely been established that certain pituitary extracts produce a glucocorticoid type, others a mineralocorticoid type of reaction. Furthermore, in response to stress, the pituitary itself may discharge predominantly glucocorticotrophic or mineralocorticotrophic principles.

The mineralocorticoids share with the glucocorticoids the ability to increase the general resistance of adrenalectomized animals They also cause severe lesions in the kidney if large quantities of them are given over a long time There is distension of the convoluted tubules, proliferation of the spiral segments, hyalinization of the glomeruli, proteinuria, hyalin-cast formation, and, eventually, nephrosclerosis.

It is highly probable that mineralocorticoids increase renal pressor substances production especially through some direct functional effect upon the convoluted tubules. Even the subsequent morphologic changes in this part of the nephron precede the development of glomerular sclerosis. Eventually, however, the gradual constriction of the glomerular capillary bed acts somewhat like the Goldblatt clamp or the "endocrine kidney" operation, and

simultaneously with the inhibition of glomerular filtration, increases the endocrine activity of the nephron. At the same time, the inactivation of renal pressor substances is impeded and a hormonally induced renal hypertension ensues

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Damage and Other Factors Conditioning Defense

As we have said before, many nonspecific actions of stressors merely represent manifestations of damage and are not mediated through either the humoral or the nervous defense systems outlined above. These changes appear to result from necrobiosis of cells not sufficiently protected by the systemic defense mechanism. Thus, tissue catabolism occurs under conditions of stress even in the absence of the pituitary, the adrenals, or the sympathetic nervous system. Although glucocorticoids enhance catabolism, especially of readily dispensable proteins, e.g., that of the thymus, the lymphnodes, and connective tissue, extensive losses of body protein, fat and carbohydrate can occur even after adrenalectomy.

Catabolites, thus produced, can condition the defensive chain-reaction of the G-A-S at various links. We have seen that protein tends to favor the mineralocorticotrophic type of hypophyseal discharge, that sodium increases, while renotrophic steroids decrease the sensitivity of the kidney to overdoses of mineralocorticoids, that topical chemical irritation augments the fibroplastic and hyalinosis-producing action of mineralocorticoids, and so forth. There is every reason to believe that endogenously liberated protein (or amino acids), sodium, renotrophic steroids, and irritating metabolites would influence such hormone actions in the same manner as these substances do when they are exogenously introduced into the body. The intensity and the quality of such endogenous self-conditioning of the G-A-S largely depends upon the body's reserve of these metabolites and the intensity with which they are discharged into the blood Presumably, this in turn is influenced by heredity, species differences, previous exposure to stress, the nutritional state of the organism, etc.

We saw that the specific actions of individual stressors may likewise act as conditioning factors Thus, agents causing intense renal damage can sensitize the body to the pressor effects of the G-A-S somewhat in the same manner as partial nephrectomy does; pyrogens, histamine, and other stressors capable of causing severe vascular paralysis will selectively "decondition" the arterial tree to the pressor action of endogenous renal pressor substances; microbes, allergens, or local mechanical trauma can stimulate the tissues which come into direct contact with them (somewhat like the formalin or mustard in our "topical irritation arthritis" test) to the formation of a fibroplastic and hyalin-containing granuloma tissue

Such conditioning factors affect the defense mechanism at different points and may either increase or decrease the efficacy of any one among its individual components. Hence, it is evident that the essentially stereotypical defense pattern of the G-A-S can manifest itself in widely different ways, depending upon such conditioning factors

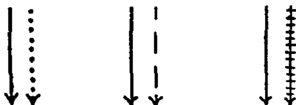
This is particularly important for the understanding of the diseases of adaptation. Unless conditioning factors could considerably alter the reaction-pattern to stress, it would be impossible to ascribe rheumatoid arthritis, periarteritis nodosa, allergies, certain types of diabetes, or hypertension to the same causative agent, namely to systemic stress. The concept that such widely different maladies should result from the same cause has often been

considered to be quite contrary to accepted views concerning the causation of disease. Since this tenet is rather fundamental for our interpretation of the diseases of adaptation, it deserves special attention.

Let us point out first that such an assumption is not without precedent in medicine For example, excessive production of thyroid hormone may be associated with predominantly ophthalmic, metabolic, or cardiac derangements. Before the tuberculosis bacillus had been isolated, it would have been considered most improbable that such dissimilar conditions as Pott's disease, phthisis of the lungs, miliary tuberculosis, and the tuberculous lupus of the skin are all caused by the same pathogen; yet, this is the case.

We have attempted to demonstrate that the polymorphism of the G-A-S symptomatology is due to two principal reasons. First, every stressor has specific actions in addition to its stress-producing ability. The former modify the response caused by stress as such; hence, the polymorphism of the G-A-S manifestations can be due to specific effects of the evocative stressors.

The following schema will illustrate this point. In all three figures the solid arrow represents stress, the other the "contaminating" specific actions.



Obviously, the end results of exposure to the three agents represented here could not be the same.

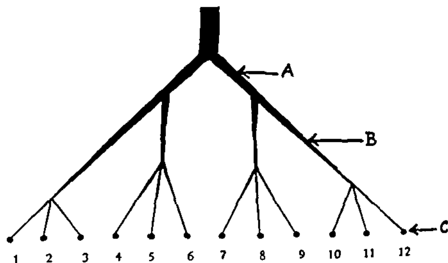
This type of conditioning may also be illustrated by an example taken from chemistry All acids have many properties in common, yet the reactions of each member in this group are essentially different The characteristics which they share are due to their acidity; the properties which distinguish them are the specific reactions of the carriers of this acid function. In pharmacology, the stressor effect is what the drugs have in common; their other properties endow them with specific pharmacologic actions Both in chemistry and in pharmacology, the specific properties condition that non-specific feature (acidity, stress) which the entire group shares. Hence, no two acids—and no two stressors—act exactly alike This may help to illustrate conditioning by specific properties of the stressor

We have seen, however, that even exposure to the same stressor agent may result in qualitatively different responses Here, polymorphism of the G-A-S manifestations is due to selective conditioning by factors extraneous to the stressor. This peripheral conditioning may occur at the various intermediate stations of the G-A-S or in the target organs themselves. We have compared this to the manifold effects one can obtain with the same electric current During an emergency, it may be necessary to supply more electricity for a community. This current will always be of the same quality and it will always travel along the same, pre-existent, main channels. Yet, depending

upon the kind of emergency and the special needs of each district, both its quality and quantity has to be regulated locally in the periphery. Thus, the same current can be used to produce mechanical work, sound, light of any color, heat, or cold, and indeed, it may be shut out completely from a locality where it would represent a fire hazard. Of course, the more we approach the periphery of such an electric circuit, the more subject it will be to conditioning, first, because the thin terminal wires can more easily be handled than the thick principal cables, and second, because interventions anywhere along the line, above such a peripheral point, would affect the latter.

Essentially, the same is true of the G-A-S. The more we approach the periphery, the more often do we note deviations from the standard G-A-S pattern. All stressors cause an ACTH discharge, but this may or may not be accompanied by the production of the "X factor," which is necessary for mineralocorticotrophic actions. Interference at a lower level may cause even more selective deviations from the typical stress response. Thus, transection of the splanchnics may impede epinephrine discharge during the Alarm Reaction without interfering with any G-A-S manifestations except those resulting directly from hyperadrenalinemia. Possibilities for conditioning become ever more selective as we approach the peripheral target organs, each of which can be individually protected or sensitized to the typical actions of the G-A-S.

It is an inherent characteristic of most ramifying systems that side branches are more readily influenced than main lines. The following schematic drawing will help to illustrate this.



[illegible] target organs
[illegible] would
[illegible] ts us to
[illegible] he one
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Principal Criticisms of the G-A-S Concept

The general outlines of the G-A-S concept have not been challenged, but some of its aspects became the subject of much debate and criticism; these deserve special consideration here.

Why are the "diseases of adaptation" so polymorph in their manifestations if they are all due to stress?—We mention this question only for the sake of completeness, since it has already been answered in the preceding section. We believe that the principal reasons for this polymorphism are the so-called conditioning factors, namely, the specific effects of the evocative stressors and other exogenous or endogenous factors (heredity, pre-existent disease of certain organs, diet, previous exposure to stress, etc.) which can affect, selectively, certain pathways or target organs of the G-A-S response.

Why does exposure to the same stressor produce disease only in certain individuals?—It is undoubtedly true that the same drug, microbe, emotional irritant or physical injury may produce a disease of adaptation in one person and be tolerated with impunity by another. It should be recalled, however, that the G-A-S is a useful, normal physiologic reaction to stress; only its derailments have been interpreted as diseases of adaptation. Hence, exposure to a stressor can be expected to produce such diseases only if the defense reaction is inadequate. Thus, for instance, in our experimental efforts to produce the hyalinosis-hypertension syndrome in rats by exposure to cold, we found it necessary to perform unilateral nephrectomies and to keep the animals on high-sodium, high-protein diets. All these conditioning circumstances failed to produce disease in the absence of stress, but upon exposure to cold, they caused a derailment of the G-A-S with consequent cardiovascular lesions, nephrosclerosis, and a rise in blood pressure. It is very probable that in man also, under the influence of stress, similar diseases would develop only when the G-A-S is prevented from evolving in a normal manner, as a result of adverse conditioning factors

Desoxycorticosterone may not occur in the adrenals.—The fundamental work concerning the diseases of adaptation has been performed in animals treated with excesses of DOCA It is this work which led to the concept that diseases could be due to an excessive mineralocorticoid production. Yet, evidence now at hand is insufficient to prove with certainty that desoxycorticosterone is produced, as such, by the adrenal cortex

It will be recalled that LAP (a mineralocorticotrophic extract) also causes similar lesions in intact, though not in adrenalectomized, animals Even if desoxycorticosterone itself were not secreted by the suprarenal cortex, the above observations would still strongly suggest that some similarly acting principle is produced as a result of hypophyseal stimulation. Furthermore, the "amorphous fraction" of Kendall, the "sodium factor" of Hartman, and desoxycortisone have all been shown to possess typical mineralocorticoid actions All these substances have been prepared from the adrenals by several investigators and in good yields, so that there can be no question about their being natural products of suprarenal activity.

The doses of desoxycorticosterone acetate (DOCA) used in the fundamental experiments on the "diseases of adaptation" may exceed the amounts produced endogenously, by the adrenal itself.—This criticism has been voiced particularly with regard to the earliest experiments, in which DOCA was given in the form of injections to nonsensitized animals. Subsequently, with the introduction of the pellet implantation technique especially in animals sensitized by unilateral nephrectomy and/or high-sodium diets, much smaller amounts of the hormone proved to be disease-producing.

It must be remembered, furthermore, that there is no objective reason to consider the pathogenic amounts of mineralocorticoids as being beyond the limits of what could be produced in the body during stress. The quantities excreted in the urine of men who had received DOCA in doses conducive to hypertension, increased blood volume, edema, and renal damage do not exceed those eliminated by patients after burns, traumatic injuries or acute infections. If we can judge by the amounts of glucocorticoids required to produce remissions, in those spontaneous diseases which have been simulated in the animal by DOCA overdosage, then this criticism appears to be even more unjustified. About 10 mg. of DOCA per day given over a period of weeks would certainly be pathogenic in man, while 80 to 100 mg of cortisone are usually required to produce a pronounced remission, for instance, in rheumatoid arthritis or lupus erythematosus. Furthermore, even normal amounts of mineralocorticoids could result in derailments of the G-A-S if their effects upon certain target organs was abnormally increased by the actions of a pathogen.

How can one reconcile the fact that the "rheumatic-allergic type" of disease is produced by corticoids in animals and nevertheless responds so favorably to corticoid therapy in man?—This question hardly deserves much comment now, although it was asked just after the introduction of cortisone into clinical practice. The original animal experiments, of necessity, had to be performed with DOCA (a mineralocorticoid) since this was the only adrenal steroid available in adequate amounts. Its effects upon many target organs are the reverse of those produced by glucocorticoids, e.g., cortisone. As we now know, this is due partly to a peripheral antagonism at the level of the target organs themselves and partly, perhaps also, to the inhibition by glucocorticoids of mineralocorticoid production through the "compensatory atrophy" phenomenon

The urinary elimination of corticoids is not always demonstrably abnormal in the diseases of adaptation—As we have repeatedly emphasized, diseases of adaptation do not necessarily result from an absolute deficiency or excess of corticoids; they can also ensue as a consequence of an-improper balance between gluco- and mineralocorticoid secretion or be caused by a state of relative hypocorticoidism. Thus, in our "topical irritation arthritis," the introduction of an irritant into the joint region produced a violent arthritis in perfectly normal animals, yet it failed to do so after pretreatment with an excess of ACTH or cortisone. This clearly shows that the adequacy of cor-

ticoid production can only be assessed in proportion to the pathogen which creates a need for such hormones It is highly probable that pathogenic factors, which cause disease in individuals whose corticoid production remains normal would fail to do so if the adrenals responded with an increase in hormone discharge commensurate with the increased requirements occasioned by an abnormal situation. Indeed, it is quite possible that many individuals who carry the pathogens (whatever these may be) of rheumatoid arthritis, allergies, lupus erythematosus, and so forth can remain in perfect health throughout life because through the G-A-S mechanism, they have rendered these potential pathogens quite innocuous To use an analogy from an entirely different field, one might compare them with the typhoid or meningococcus carrier who lives in perfect harmony with the deadly germs present in his body.

It should be mentioned, furthermore, that some evidence of an anomaly in steroid metabolism has been noted in patients suffering from the rheumatic-allergic diseases, e g., increased pregnandiol excretion after the administration of progesterone, anomalies in 17-ketosteroid elimination. Research along these lines has been handicapped principally by the difficulty of assaying blood or urine specifically for mineralocorticoid activity. However, several recently published improvements in the relevant techniques hold great promise as regards the elucidation of this important problem.

Clinical Applications of the G-A-S Concept

As regards clinical medicine, we feel that the principal value of the G-A-S concept is that, by helping to understand the rôle of the stress factor in disease, it enables us to adjust our therapeutic measures accordingly

Nonspecific therapy—It becomes increasingly more evident that many of the time-honored, though not spectacularly effective, nonspecific therapeutic measures, such as fever therapy, shock therapy, parenteral administration of foreign proteins, blood-letting, or mere starvation, are beneficial, largely, through the G-A-S Often their principal value appears to be that they stimulate ACTH and glucocorticoid production Wherever this is so, it may be preferable in the future to inject ACTH or cortisone In certain instances, however, nonspecific therapy proved efficacious where ACTH failed. For instance, in mental patients, who did not respond to ACTH, it could be shown by subsequent shock therapy that they are benefited by nonspecific stress Here, presumably, certain specific changes incident to the shock act together as conditioning factors of the hypophysis-adrenal discharge or separately through other channels of the G-A-S, e g., the nervous system or the catabolic response of the Alarm-Reaction

There is a striking parallelism between the diseases empirically shown to respond to nonspecific therapy and those which show dramatic remissions under the influence of ACTH and cortisone, e g , rheumatoid arthritis, various inflammatory conditions of the eye, allergies Through the use of the corticotrophic and corticoid hormones, we are on the threshold of developing

a modern version of nonspecific therapy which is much more effective than the old and lends itself better to a scientific analysis of its mechanism.

Dietary treatment of cardiovascular and renal diseases.—Diets poor in seasoning (spices, salt) and/or protein have long been recommended in the treatment of hypertension, nephritis, nephrosis, and allied conditions However, the results were rarely spectacular and, in the absence of any convincing rationale which could justify their use, they have not been received with sustained enthusiasm. Purely empirical observations on a heterogeneous clinical material failed to show clearly even whether the detrimental effects of highly seasoned food are due to sodium, chloride, or condiments in general. It also remained a subject of debate whether certain vegetable proteins are more readily tolerated than meat and especially whether, in the face of heavy urinary protein losses in renal disease, it is better to prescribe low-protein diets to protect the kidney against overwork or rations rich in protein to substitute for the constant urinary losses.

A study of the mechanism through which stress causes cardiovascular and renal disease has established certain definite facts concerning the rôle played by protein and minerals in the pathogenesis of the experimental replicas of such maladies. If these data can be applied to the corresponding clinical diseases, and there is much reason to think that they can, then we shall soon be able to prescribe diets on a much more rational basis. Now that we know how to reproduce these diseases in animals, it is comparatively simple to establish the pathogenic rôle of each dietary constituent under rigorously controlled experimental conditions.

Corticotrophin and corticoid therapy—Undoubtedly, the most important pertinent data are those derived from the clinical use of ACTH and cortisone. Since only very limited amounts of these hormones have been available up to date, it is not yet possible to assess their scope accurately. However, it is precisely now that some general orientation in this field is most urgently needed By way of a summary, let us say, therefore, that apart from their obvious utility in hypocorticoidism and anterior-pituitary deficiency, ACTH and/or cortisone have been shown to excite an effect in the following conditions: agranulocytosis, alcoholism, allergies (various, in addition to those specifically mentioned here), allergic rhinitis, asthma, atopic dermatitis, blepharitis, choroideremia, choroiditis, conjunctivitis vernalis, dermatomyositis, drug sensitization, eczema, exfoliative dermatitis, erythema multiforme, fevers (apparently irrespective of etiology, though probably normalization of the temperature is not always an advantage), gouty arthritis, hay fever, hemolytic anemias of various kinds, herpes zoster, Hodgkin's disease, idiopathic hypoglycemia, iritis, iridocyclitis, keratitis, leukemias (various), Loeffler's syndrome, lupus erythematosus disseminatus, lymphosarcoma, nasal polyps, nephrosis, neurodermatitis, ophthalmologic conditions (especially those characterized by allergic and inflammatory manifestations), periarteritis nodosa, pneumonia (pneumococcus, primary atypical), psoriasis, retinitis (centralis, pigmentosa), retrobulbar neuritis, rheumatic fever, rheumatoid arthritis and spondylitis, serum sickness, tuberculosis of

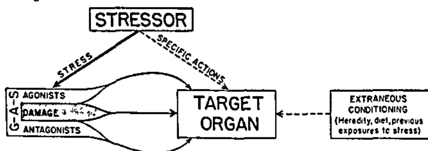
the larynx, ulcerative colitis, urticarias (various), uveitis, and vasomotor rhinitis.

Preliminary data suggest that this type of treatment may also be effective in the following conditions: Boeck's sarcoid, glaucoma, hepatitis, hypertension, hyperthyroidism (especially in normalizing the basal metabolic rate and reducing the exophthalmus), keloids, liver cirrhosis, myasthenia gravis, nephritis (especially if due to allergy), pemphigus, scleroderma, and thromboangiitis obliterans (Buerger) Available data suggest that ACTH and/or cortisone are of no value in amyotrophic lateral sclerosis, carcinomas of most types, congestive heart failure, diabetes mellitus, multiple myeloma, poliomyelitis, and multiple sclerosis.

ACTH and/or cortisone may produce harmful effects in acne vulgaris, congestive heart failure, Cushing's syndrome, diabetes mellitus, hypertensive disease of certain types, nephritis of certain types, osteoporosis, peritonitis, septicemia, and wound healing. In this connection, it should also be emphasized that, under certain conditions, ACTH and/or cortisone may actually cause acute pulmonary edema, ascites, marked decrease in resistance to infectious, and obscuring of the criteria of disease, e g , fever and abdominal rigidity in peritonitis, the hematologic manifestations of systemic diseases, the acceleration of the pulse in acute infections, etc.

Diagrammatic Synopsis of the G-A-S Concept

And now, in the last few paragraphs of this review, I should like to summarize concisely what appears to me its most important outcome. All agents can act as stressors producing both stress and specific actions. No agent can produce one without the other. The specific actions affect the target organs in a variety of ways. Stress acts only through the G-A-S. It causes defense and damage



The defense mobilizes agonists and antagonists which, through their interaction on the target organ, stabilize the latter and adjust its response to injury. But stress also invariably causes some degree of damage through the G-A-S. This likewise affects the target organ, though not through the humoral and nervous mediators of nonspecific defense

Factors extraneous to the G-A-S, e g , heredity, diet, previous exposure to stress, can condition these responses. Thus, in the final analysis, the reac-

tion of the target organ will depend upon the specific actions of the stressor, the effects of the resulting G-A-S (agonists, antagonists, nonspecific damage), and extraneous conditioning factors This explains how the essentially stereotypical G-A-S response can lead to a variety of polymorph syndromes and why so many apparently unrelated diseases are amenable to therapy by "stress hormones."

Disease consists of two components, damage and defense. Up to now medicine has attempted almost always to attack only the damaging pathogen (to kill the germs, to excise tumors, to neutralize poisons). As regards defense, hitherto medicine limited itself to such vague advice as the usefulness of rest, wholesome food, etc. A study of the G-A-S suggests that henceforth we will be able to rely upon much more effective means of aiding adaptation to nonspecific local or systemic injury by supplementing the natural defensive measures of the G-A-S, whenever these are sub-optimal.

Addendum

While this article was being composed, we have been able to show that electrophoretically pure growth hormone causes hypertension, myocarditis, and nephrosclerosis in the rat under suitable experimental conditions This suggests that the hitherto unidentified "X factor" in our crude anterior pituitary preparations is identical with, or produced under the influence of, growth hormone.

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NEOPLASTIC DISEASES[1,2]

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Because many different phases of cancer therapy have been brilliantly reviewed within the last two years, no attempt will be made here to resummarize work, even though it is per se of intrinsic significance in the treatment of neoplastic disease Brief mention of available summaries will suffice to orient the reader in relation to this mass of valuable material We shall, therefore, merely indicate the character of various reviews without attempting to examine the large fields which they cover and then proceed to outline more recent work in the field of endocrine treatment which deserves another summary

A valuable *Index of Tumor Chemotherapy* recently prepared by Dyer (1) lists all the substances tested in experimental tumor therapy It is of monumental proportions, containing 2,213 references, and constitutes an almost essential laboratory handbook. Material concerning carcinogenesis, the nature of the tumor cell, and the relation of tumor cell to host was reviewed last year by Shimkin (2) along with the latest therapeutic developments With Bierman, Shimkin outlines available procedures and classifies them according to site of evoked response (3). They fall into four general categories: (*a*) procedures which attack some physiological function retained by the cancer cells themselves, e g, iodine retention in thyroid tumors, (*b*) procedures which alter the biochemical substrate of the tumor which still remains dependent on its environment, (*c*) procedures which destroy or inhibit bone marrow or circulating cells, and (*d*) procedures which injure the vascular supply of the tumor, e g, the use of *Bacillus prodigiosus* polysaccharide. The trends in experimental chemotherapy of neoplastic disease and the agents which appeared to be of clinical value in 1948 have been discussed by Karnofsky (4) In a more recent publication with Burchenal (5), he extends this outline through 1949 and provides a very large, detailed bibliography These two authors conclude from their survey of the literature that there is parallelism between the response of the cells of Hodgkin's disease to x-ray and to nitrogen mustard They state that "there is no evidence for the idea that tumor cells may be resistant to x-ray but responsive to HN_2 or vice versa." Gellhorn & Jones (6) cover much the same ground in a very comprehensive article which reviews the various therapeutic methods historically and provides many references to source material Other excellent general reviews have also been published by Reinhard, Good & Martin (7) and by McKee (8). Evalua-

[1] The survey of the literature pertaining to this review was concluded in November, 1950

[2] This is publication No. 727 of the Harvard Cancer Commission.

tion of therapeutic methods and suggestions about diagnostic procedures are considered in a survey article by Homburger (9) which appeared in January, 1950 Dodds (10) summarizes work in a smaller field, emphasizing the manner in which various agents produce their effects Drugs like diethylstilbestrol are reported to alter the environment so that tumors cannot flourish, while a second group such as colchicine and urethane are cytotoxic in action; still others prevent mitosis, and the nitrogen mustards appear to influence nuclear metabolism. Much the same ground is covered by Snapper & Greenspan (11). They include an interesting discussion of results obtained experimentally with 2-hydroxystilbamidine. This drug is reported to enter the cell nuclei of certain normal tissues (liver, kidney, testicles, and adrenals) in considerable amounts and to show a similar specificity toward some neoplastic tissues It enters the cell nuclei of transplanted hepatomas with relative ease, but only traces can be found in the cell nuclei of transplantable lymphosarcomas and adenocarcinomas of mammae. Present knowledge of the clinical usefulness of adrenocorticotrophic hormone (ACTH) and cortisone in many disorders, including neoplastic disease, has been clearly summarized by Thorn, Forsham and their co-workers (12) in a comprehensive survey.

Throughout these reviews, there seems to be general consensus of opinion that progress is being made in the field of cancer chemotherapy. Although none of the procedures now known can cure cancer, some exert at least transitory effects on the course of tumor development. Certain of the newer therapeutic measures preferentially destroy many cells, but obviously not all, in specific tumors. To explain this, Gellhorn & Jones (6) assume that "among the cells of a susceptible tumor there is variation in resistance to the cytotoxic agent which may be a primary or an acquired characteristic."

ACTH, CORTISONE, AND NEOPLASTIC DISEASES

Before entering into a discussion of the most recent clinical experience with endocrine compounds in the treatment of cancer, it is desirable to consider certain experimental work which has led to the development of clinical procedures with adrenocortical preparations. Since the production of adequate amounts of Compound E (cortisone) and of the pituitary adrenocorticotrophic hormone (ACTH) a large number of investigations have been carried out. The work is so new that many reports have not yet been published except in the form of very brief abstracts. It seems worthwhile, however, to consider these in this survey because many of the studies are significant. Since the action of cortisone and of ACTH on tumors appears at this early date to be quite analogous, no attempt will be made to discuss the effects of these two drugs separately. It should be clearly kept in mind, however, that ACTH increases the production of other adrenal hormones as well as cortisone and produces hypertrophy of the adrenal cortex, while the administration of cortisone may lead to adrenocortical atrophy. These compounds are both most effective in influencing tumors of the lymphatic series

of cells, and this one would have expected from older observations on, for instance, the relation between the adrenal, the thymus gland, and the lymph nodes.

Heilman & Kendall (13) were the first to publish data about the effect on neoplasia of the adrenocortical substance known at first as Compound E and later as cortisone They withheld their original paper from publication from 1942 until 1944 so that they might verify results. Working on two malignant tumors of the lymphosarcoma type in mice, these investigators found that Compound E produced dramatic but transitory results. After a few weeks of improvement, the tumors recurred and were then found to be unresponsive to further doses of the drug Heilman & Kendall at that time concluded that this form of treatment was unsuitable.

Sugiura, Stock, Dobriner & Rhoads (14) have published the results of an extensive study of the effects of cortisone acetate (Compound E) and other steroids on the growth of many transplantable mouse tumors, mostly not lymphatic Daily injections were given subcutaneously for one week, the first injection being made on the day following implantation of the tumor.

Cortisone acetate (37 5 mg/kg day) in aqueous suspension caused a marked inhibition [illegible]

test, despite relative weight losses in the treated animals

Stock (15) has continued these experiments and, in his brief report of the longer study, states that cortisone inhibits growth of osteogenic and lymphogenous sarcomata by slowing growth and lengthening survival Compounds F and A of the adrenal are also actively inhibitory while many other steroids do not affect the progress of the mouse and rat tumors. In work by Higgins, Woods & Bennett (16), the influence of cortisone on the growth of rhabdomyosarcoma in C3H mice was studied Growth of the tumors was completely inhibited in animals which received 1 0 mg. of cortisone intramuscularly on the day following implantation and daily thereafter. When this medication was discontinued on the eighth day after implantation, the tumors grew and continued to grow until cortisone therapy was reinstituted at the end of a week. This second course of medication restricted further growth of the tumors, but did not seem to cause regression

Stoerk (17) and Emerson (18) observed regression of lymphosarcoma transplants in riboflavin-deficient mice and resistance of these mice to subsequent transplants of the same tumor At the ACTH-Adrenocortical Steroid Conference of the American Cancer Society, Stoerk (17) reported that this acquired immunity diminished during the hyperadrenal state and during pyridoxine deficiency in rats He stated that administration of cortisone or the induction of pyridoxine deficiency prevents this regression of the tumor in lymphosarcoma-bearing rats which are deprived of riboflavin Emerson, Wurtz & Zanetti (18) report that in mice with well established lymphosarcoma transplants, administration of cortisone caused rapid regression of the

tumors, while in riboflavin-deficient control animals, the tumors were still apparent 10 days after implantation. There was, however, no evidence of summation of the effect when cortisone was administered to animals with a dietary riboflavin deficiency.

Schoenbach (19) studied the effect of adrenocortical substances on a transplantable stem cell leukemia (L1210) in mice. He reports that cortisone, but not ACTH, appeared to inhibit development at the site of implantation. Neither compound altered the course of the disease or augmented the effects of aminopterin

Karnofsky, working with embryonic chicks, newborn chicks, and mice (20), has observed a remarkable inhibition of normal growth following administration of various adrenocortical compounds, particularly Compound F acetate. In the egg, retardation of growth becomes evident on the eighth day of development

Turning now from laboratory studies to reports of clinical work, we find a greater volume of available material and greater variety of result Observations have been made on patients of widely differing age with tumors of many types The observations of Dougherty & White (21), reported in 1943, were followed by a recent study at Memorial Hospital in New York of a group of patients with lymphatic tumors Pearson, Eliel & Rawson (22, 23) reported the effects of cortisone and ACTH in a series of seven adult patients: three with chronic lymphatic leukemia, one with follicular lymphosarcoma, one with Hodgkin's disease, one with carcinoma of the prostate, and one with metastatic carcinoma of the breast. Cortisone acetate was also given to one patient with chronic lymphatic leukemia. The dosage was comparable in all instances, that of ACTH being 100 to 200 mg. daily for 18 to 30 days. In the six patients with lymphomatous tumors, there was dramatic progressive decrease in the size of lymph nodes and spleen Some of the improvement lasted for a matter of weeks, and in some cases, there was further response to a second course of treatment In the patients with lymphatic leukemia, on the contrary, the white blood cell count rose markedly during the course of medication only to fall again during or after treatment Laboratory tests showed that the potassium, phosphorus, nitrogen, and calcium balances were consistently negative in all patients, while both sodium and chloride balances were positive Histological examination of lymph nodes in three patients before and after administration of ACTH revealed no histological changes in individuals with lymphatic leukemia, whereas, after medication in the patient with lymphosarcoma, there was disappearance of germinal centers and decrease of cellularity No complete clinical remission followed treatment with cortisone and ACTH The two cases of carcinoma did not seem to respond to the injections

Dobriner and his associates (24) state that in patients with neoplastic disease, the excretion of adrenocortical and gonadal steroid metabolites is markedly diminished and that often certain steroids are no longer demonstrable; they therefore think that there may be a gonadal and adrenal dys-

function in patients with malignancy. To determine the effect of stimulating the adrenal, they measured the excretion of ketosteroids and formaldehydogenic steroids before and after the administration of ACTH. Tests for individual ketosteroids as well as gross analyses rose essentially normally after medication, a finding which indicates clearly that adrenal activity can be increased in patients with cancer and lymphoma. These workers conclude from their observations that although there is great difference in the response of different individuals to a given amount of ACTH (100 mg.), the general trend of steroid, nitrogen, and electrolyte excretion after medication is roughly parallel, i e , when one increases, the others increase also.

Taylor and his co-workers have published two reports of clinical work with ACTH and cortisone (25, 26) The earlier of these describes results obtained in two cases of advanced carcinoma of the breast with metastases, one case of mycosis fungoides, one of carcinoma of the trachea, and one of Ewing's tumor. In no instance except in the case of mycosis fungoides could any regression of the disease be attributed to the effect of ACTH alone, although fever and discomfort were alleviated by the medication. In the patient with mycosis fungoides, the itching disappeared, but histological examination showed that the disease remained active The later report deals with the effect of ACTH and cortisone on 26 patients with far advanced malignant disease, nearly all of whom had previously received the usual types of treatment In this group, there were various forms of carcinoma, sarcoma, hypernephroma, melanoma, multiple myeloma, and various forms of lymphocytic disease In the cases of carcinoma, melanoma, and myelogenous leukemia, the drugs appeared to exert no regressive effect on the neoplastic growth. The cells were viable and actively proliferating. Reduction of the size of skin lesions and healing of ulceration, which seemed to result from treatment with cortisone in one case of carcinoma of the breast, persisted only for about four weeks. In three of the four cases of carcinoma of the breast, tumor growth appeared to be augmented by treatment, although induration and edema around the site of the tumor frequently diminished. Biopsy tests made after treatment with ACTH revealed no changes in peripheral blood or bone marrow in the patients with melanosarcoma, subacute myeloid leukemia, and acute leukemia (in a child), no changes in the nodes of a patient with chronic leukemia, and no changes in the bone marrow of an individual with multiple myeloma. In Hodgkin's disease on the other hand, there was major regression in the size of the tumor, although the histological picture changed but little. Spleen, liver, and tumor masses, etc , may be reduced in size by treatment and remain smaller for several months, as in lymphosarcoma. The response to ACTH of two patients with mycosis fungoides was not identical In one, there was 90 per cent regression and healing of the lesions; in the other, only 10 per cent. Cortisone evoked a better response than ACTH in this latter individual The conclusion seems warranted that these drugs exert little effect on neoplastic diseases, although in most patients, they produce a striking temporary improvement of the general

condition. In other words, this work seems to bear out the suggestion of Thorn and his associates (12) that ACTH and cortisone may influence the tissues surrounding the tumor rather than the tumor itself.

Investigators working with Spies (27) on 10 patients (inoperable squamous cell carcinoma, three; acute leukemia, five; lymphosarcoma, two), found that nine responded to ACTH treatment with amelioration of symptoms and dwindling of the lesions, although the disease did not disappear in any case. The fact that histologically the underlying lymphosarcoma did not change was of special interest because the nodes became smaller, fever disappeared, appetite returned, and the patient seemed better clinically while pathological findings remained unaltered. When clinical symptoms recurred, these patients responded again to further treatment.

In multiple myeloma, results of different studies with ACTH are far from uniform, but there seems to be no consistently favorable response (12, 28 to 30). In one very sick patient who received 80 mg ACTH daily for 20 days, marked clinical improvement, a dramatic fall of the elevated serum globulin from 10 2 gm. to 4.8 gm. per 100 cc., and disappearance of plasmoblasts from the bone marrow, as well as increase of osteoblastic activity and higher blood hematocrit values have been observed by Thorn and his associates (12). The course of the disease in this patient after cessation of ACTH therapy remains to be determined, but Pearson and his group reported that it seems likely that the reaction of the immature myeloma cell is analogous to that of lymphocytes (28) Of the five cases reported by Dameshek (29, 30), only one showed definite improvement after administration of ACTH. This patient had failed to benefit from urethane, but laboratory tests gave evidence that the improvement attributable to ACTH was maintained for six months.

Three patients with advanced multiple myeloma have been treated with ACTH by Kelley, Nathanson & Aub (31). One showed marked prolonged response to this therapy, one an equivocal response, and the third no response. Before administration of ACTH, the first patient had marked anemia which did not respond to transfusion, bone pain, and kyphosis. Extensive osseous lesions were revealed by x-ray. Serum globulin was elevated, Bence Jones proteinuria was present, and the bone marrow showed a preponderance of plasma cell elements, the majority of them plasmoblasts and plasmocytes. ACTH was given in 80 mg. daily doses for one month followed by 60 mg. daily doses for one month. The patient improved steadily both subjectively and objectively throughout the treatment period and has maintained satisfactory status for six months without further treatment. During the course of ACTH administration, hemoglobin rose 5.5 gm , and there was a corresponding rise in hematocrit figures. Serum globulin diminished from 11.2 gm per cent to 3.4 gm per cent; urinary Bence Jones protein became virtually undetectable. The bone marrow showed marked erythroid stimulation and a significant decrease in the proportion of plasma cell elements, with a shift to the right of those which remained. The usual metabolic effects of negative nitrogen, calcium, and phosphorus balance and hypochloremic, hy-

pokalemic alkalosis were observed. No toxic manifestations or Cushing-like alterations were noted. X-ray appearance of osseous lesions remained unchanged.

Prior to treatment, the second patient had anemia, mental derangement, hyperglobulinemia, Bence Jones proteinuria, and widespread osseous and soft-tissue invasion by myelomatous tissue. Marrow aspiration revealed large numbers of mature "myeloma cells." ACTH was administered for one month in daily doses of 100 mg. with no favorable clinical, hematological, physiological, or pathological effect. The patient died a few days after cessation of treatment. At necropsy, myelomatous tumors were found to be widely disseminated throughout bone, abdomen, chest, and pelvis. A third patient currently under treatment shows a predominance of proplasmocytes in marrow. There is no anemia, but hyperglobulinemia, Bence Jones proteinuria, and widespread osseous involvement are present. After three weeks of treatment with daily doses of 100 mg. ACTH, there is some relief of bone pain, some improvement of appetite, and a slight fall in serum globulin. The bone marrow pattern has not been altered. The response of these three patients illustrates the variety of reaction to ACTH in multiple myeloma and corroborates the contradictory reports appearing in recent literature on the subject

Temporary and not very dramatic response has been seen in cases of lymphosarcoma and Hodgkin's disease already incorporated in this report. Schoenbach (19) thought that patients with Hodgkin's disease derived little benefit from treatment with ACTH, although subjective improvement and loss of fever sometimes occurred. He found no advantage in alternating ACTH with cortisone or combining these drugs with nitrogen mustard treatment At Huntington Memorial Hospital, Kelley, Nathanson & Aub (31) have administered ACTH to three patients with Hodgkin's disease and to one with advanced lymphocytic lymphoma and chronic lymphatic leukemia. In the latter case and in one case of advanced Hodgkin's disease, ACTH appeared to hasten death One patient with Hodgkin's disease which predominantly involved the spleen and liver was given 100 mg of ACTH daily for 28 days There was satisfactory response to the drug as evidenced by diminution in the size of spleen, liver, and nodes and a rise in the hemoglobin As yet no figures for the posttreatment period are available. In the third patient with Hodgkin's disease, the chief disturbance was bone marrow depression with leukopenia, anemia, thrombocytopenia, and slight lymphadenopathy. Although there was subjective improvement during administration of ACTH (100 mg daily for 10 days) to this individual, there was no objective change These facts seem to corroborate Thorn's statement (12) that "it appears probable that ACTH is able to reduce markedly the tissue reaction to the cancerous material and thus to affect the [illegible]

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chronic lymphatic leukemia, there was no response after single doses, even though twice the amount of drug was given. This suggests that lymphatic leukemia cells do not respond easily to the action of this hormone.

In the clinic as well as in the experimental laboratory, evaluation of new therapeutic agents is impossible without a background of carefully compiled data. The significance of symptomatic and laboratory changes can only be understood in the clinic when the duration of life in the disease under consideration is known. For this reason, a study made by Bierman and his collaborators (42) on lymphatic leukemia in childhood is very important. It includes 103 cases, of which 90 were classified as lymphogenous leukemia. The data on 75 patients are complete. The figures may be tabulated as presented in Table I.

TABLE I

DURATION OF LIFE IN LYMPHATIC LEUKEMIA IN CHILDHOOD

Treatment	Number of Cases	Average Duration of Survival (months)
Untreated	18	5.6
Irradiation plus Transfusions plus Antibiotics	17	5.8
Blood Transfusions only	24	6.0
Antibiotics plus Blood Transfusions	17	8.9

They show that the newer almost routine methods of medication significantly prolong life, a factor which must be taken into consideration in evaluating the effects on life expectancy of all new drugs and procedures.

SEX STEROIDS AND NEOPLASTIC DISEASES

Experimental and clinical observations relative to sex steroids as etiologic and therapeutic agents in various neoplastic diseases have been reviewed by Nathanson in a series of papers over the past six years (43 to 47a). A monograph *Endocrinology of Neoplastic Diseases*, edited by Pack & Twombly, treats in detail sex steroids and other endocrine-cancer relationships (47). These past studies indicate clearly that only certain types of neoplastic diseases can be altered in their course by the sex steroid hormones This review will attempt to summarize the salient features of past and recent observations in human beings which influence our present concepts of the problem.

effect of ACTH and cortisone on this group of neoplasia in man. A number of investigators [Farber *et al.* (32); Pearson *et al.* (28, 33)] have concluded that with these compounds, remissions could be induced in the acute leukemia of children and adults with fair regularity but that they were incomplete and temporary. Other workers conclude that all the leukemias respond irregularly to these drugs, the best results being obtained in chronic lymphatic leukemia, acute lymphatic leukemia, and in some cases of granulocytic leukemia, especially in children and young adults.

In chronic myelogenous leukemia and in monocytic leukemia, on the other hand, the effect of the drugs is of doubtful benefit. Pierce has treated 19 cases of acute leukemia with ACTH (34) In 12 of these cases, there was complete clinical and hematological remission which lasted from 2 to 20 weeks after the first course of treatment with ACTH. This group included 9 of the 11 new cases subjected to treatment. A second remission lasting four to eight weeks was observed in five patients Bone marrow biopsies showed evidence of regeneration of both erythroid and myelocytic elements with specific stimulation of erythropoiesis. Donohue and his co-workers (35) report somewhat similar results. According to Schulman (36), no relation could be demonstrated between response to hormone therapy and to antifolic therapy; certain leukemic patients who were resistant to one were found to respond excellently to the other. Burchenal (37) has found that individuals who were resistant to a-methopterin might respond favorably to the endocrine drugs and vice versa and has, therefore, concluded that the mechanism of action of these substances is different. Complete hematologic remission was reported by Farber and his associates (38) in 5 out of 17 children with acute leukemia who were treated with ACTH One of three children who received 100 mg cortisone daily also responded with a complete remission. All remissions were short and could not be repeated with a second course of treatment. Of five children with lymphosarcoma who were treated by these same workers, only one improved. In this child, there was a remarkable reduction of the mediastinal and abdominal masses within two days after the beginning of medication Dameshek's group of 45 patients (30) included 21 cases of acute or subacute leukemia His most satisfactory results with ACTH were obtained in children with the lymphocytic type of the disease; in adults, only occasional and very temporary benefit followed administration of the drug, although autohemolysis seemed to improve Other types of leukemia did not appear to be improved by the treatment or were even accelerated by it. Since, even in lymphocytic leukemia, the results of treatment were transitory, lasting only up to nine weeks, Dameshek thought that ACTH treatment brought "pathetic benefit." Wintrobe's results were no better (39). Albright (40) has studied chronic lymphatic leukemia in a 52-year-old man which was made worse by administration of 100 mg. of ACTH for 15 days Saunders & Adams (41) found that cortisone reduced the absolute number of circulating lymphocytes and eosinophils in normal individuals and in patients with infectious mononucleosis, while in four patients with

and ovulation, whereas the efficacy of irradiation in these respects is less certain. It is now clear that the conflicting reports of the effectiveness of radiation castration in breast cancer may be due in large measure to the dosage employed (60). The development of amenorrhea and other menopausal symptoms following irradiation of the ovaries is not a sufficient criterion for judging the degree of suppression of ovarian function. Concrete evidence by studies of the vaginal smear and urinary estrogen excretion indicates that in instances there is still residual ovarian activity (60). The effective castration dose is higher in young women presumably because of greater ovarian activity (60). There is good evidence that adequate radiation dosage, taking all factors into consideration, may be as efficacious as ovariectomy. Nevertheless, because of the uncertainty, there has been a trend in our clinics to perform ovariectomy in younger women wherever possible and to reserve radiation of the ovaries primarily for women over the age of 40 when ovarian function usually begins to decline. It is interesting that Adair *et al.* (55) and others found no significant difference in the response to ovariectomy or ovarian radiation. This poses a problem which needs further study since it is likely that ovarian function was not always completely ablated when radiation therapy was employed. If these observations can be confirmed, it is possible that only certain elements of ovarian function need be obliterated to obtain the desired effect.

Effects of castration —Improvement of physical status, rehabilitation, relief of pain, and increase in appetite and weight usually accompany, but may occur without, obvious local responses. Anemia secondary to osseous involvement may also improve. Primary, lymphatic and other soft tissue lesions of breast cancer in the female may undergo profound regression and osseous lesions may calcify following castration (54 to 56, 61). Beneficial effects of castration, whenever instituted, are of limited duration lasting for a few months to several years. Thus, the trend is to withhold the procedure for treatment of manifestations beyond effective therapy by the usual techniques of surgery and local radiation. In this way, it is possible that further benefit may be obtained and the life expectancy of the patient may possibly be prolonged.

Breast cancer in the male.—Orchiectomy in the treatment of advanced breast cancer in the male produces striking benefits similar to those seen in males with prostatic cancer (62 to 66). Although the number of cancers of the male breast available for treatment by orchiectomy is small because of the relatively low incidence, the effects are usually more obvious, consistent, and prolonged than those seen in the female. Every manifestation of the disease may undergo profound regression.

Prostatic cancer.—Huggins, in a series of monumental studies in animals and man, established the fact that prostatic cancer is androgen-dependent (67 to 71). Early studies suggested this possibility, but it required precise observations to establish the relationship (72). The historical events and the effects of orchiectomy on prostatic carcinoma are now common knowledge.

Castration

Breast cancer in the female.—Beatson in 1896 (48) and Schinzinger in 1889 (49) independently suggested that ovariectomy might favorably influence advanced mammary cancer in the female. These observations were later confirmed (50, 51). When it was discovered that x-ray could suppress ovarian function, ovariectomy was almost completely abandoned as a method of castration. The observations during the next two decades on the effect of radiation castration on advanced breast cancer were highly equivocal and disappointing As will be pointed out below, a number of the failures might be attributed to incomplete suppression of ovarian function as a result of insufficient radiation. A review of the existing data and personal experience using radiation therapy as a method of castration led Ahlbom in 1930 to take a pessimistic view of its effectiveness in the palliative control of advanced breast cancer (52). About this time, however, Aub and his colleagues observed a striking effect on osseous metastases from a breast cancer following irradiation of the ovaries in a premenopausal patient. This precipitated a systematic study of this problem which was reported by Dresser (53) and Taylor (54). Contrary to the report of Ahlbom and affirming the earlier reports, it was concluded that castration could be of definite value in the treatment of some manifestations of advanced breast cancer in premenopausal women. These studies led to a re-evaluation of the procedure in various clinics, and as a result, certain thoughts have crystallized regarding the role of castration in mammary cancer (54 to 57) These may be briefly summarized:

(*a*) Prophylactic castration. There is general agreement that prophylactic castration does not increase the curability rate of those patients in which radical mastectomy is performed for a cancer confined solely to the breast. Most observers hold this point of view even when there are axillary lymph node metastases at the time of operation A contrary opinion is expressed by Jones (57) and by Horsley (58), who advocate prophylactic castration and present data indicating an increased life expectancy and curability of the patients who have axillary lymph node involvement. It should be noted that in his series, ovariectomy was the only method used for castration. Others, using radiation as well as surgery as a means of castration, share his opinion (59).

(*b*) Therapeutic castration. There is no doubt that effective ovarian irradiation or ovariectomy may be of material value in the relief of symptoms, objective responses, and life expectancy in premenopausal patients with primary, advanced, or recurrent breast cancer. Most of the data indicate that from 15 to 30 per cent of the patients obtain palliative benefit from castration, although Halberstaedter & Hochman (56) and Sicard (59) report a higher incidence.

Method of castration —The potential effects of castration are clouded by the techniques employed to produce suppression of ovarian function. Surgery essentially guarantees permanent eradication of ovarian hormone production

duration and magnitude of palliative benefit is usually considerably greater than that seen in cancer of the breast. In fact, a significant percentage of patients remain symptomatically free, and the disease appears to be inactive for periods as long as five years or more after orchiectomy was instituted. These figures are based on the natural history of untreated prostatic cancer (94, 95) and on other forms of palliative treatment The percentage of effectiveness and the increased life expectancy in patients treated by orchiectomy have been recently summarized in papers by Gellhorn (6) and Nesbit & Baum (96).

Operability of prostatic cancer after castration.—Frequently, cancer of the prostate gland is deemed incurable by radical operation because of the local extent of the disease, even though distant manifestations are not demonstrable or may be absent. Recent studies (76, 97, 98) indicate that, in some cases, sufficient regression of the tumor may occur so as to simplify and make feasible operative removal of the tumor with the hope of a palliative if not a curative result. The preliminary results appear to be encouraging, and consequently, this aspect of the problem is receiving much more attention Transurethral resection of the prostate gland in combination with orchiectomy for advanced prostatic cancer is also being performed. In cases with severe obstructive symptoms, this has proved a valuable adjunct until and if orchiectomy is effective

Bladder cancer—On the basis of a similar embryological origin of bladder and prostatic cancer, Hebert (99) castrated four patients with extensive bladder cancer. According to his report, all had relief of pain, frequency, and hematuria. Two of the patients have survived over two years with apparent improvement in the cystoscopic appearance of the tumor Shivers (100) noted marked subjective improvement in two cases

Other cancers—Nathanson and others have attempted to influence the course of cancer of other organs by the administration or suppression of sex hormones The logic of such an approach is based on the well documented observations of sex differences in the incidence of cancer of sites additional to those originating in sex-linked organs With few exceptions, cancers common to both sexes are almost always significantly more frequent in the male. It was assumed, therefore, that removal of the major source of the dominant sex hormone might cause an alteration of these types of cancer Thus, castration has been carried out in a number of males, particularly those with cancer of the lung and gastrointestinal tract Thus far, little evidence has accumulated to verify the original assumptions It should be emphasized, however, that the number of cases subjected to castration was relatively small and that this phase of the problem needs further investigation

Adrenalectomy

Prostatic cancer—Huggins & Scott (101) adrenalectomized three patients who had a relapse of prostatic cancer following orchiectomy It was reasoned that an extragonadal source of androgens stimulating to prostatic cancer

Since the original observations, a large number of papers have appeared on this subject, providing an opportunity for a critical evaluation and the establishment of the role of castration in the palliative treatment of advanced prostatic cancer (47, 73 to 90). The fundamental studies of the Gutmans (91, 92) in establishing the relation of serum acid phosphatase to prostatic cancer have provided an important tool for an evaluation of the effects of orchiectomy and of other treatment on the disease. Furthermore, serial determinations of the enzyme may be a valuable index of the subsequent course of the prostatic cancer. The following will recapitulate and introduce newer ideas on the more pertinent effects and role of castration in prostatic cancer:

(*a*) General and systemic effects. Castration of patients with advanced prostatic cancer will frequently result in rapid and remarkable beneficial changes. Within a few days there may be complete relief of pain and beginning rehabilitation of the patient. Concomitant with these changes, there may be a significant early decline in the acid phosphatase if the initial levels are elevated. Elevated titers of this enzyme are usually found only when the disease has extended beyond the confines of the prostatic gland, but interestingly enough, the values under these circumstances may be within normal limits. The acid phosphatase levels are usually a clue to the biological activity of the tumor cells, and it has been postulated that those lesions giving rise to elevated values of the enzyme are most likely to respond to castration. Failure of an elevated serum acid phosphatase to fall is usually a bad prognostic sign and occurs in about 20 per cent of patients (93). Serum alkaline phosphatase levels are also above normal in most patients when osseous metastases are present. This is attributed to an increase in spontaneous osteoblastic activity. Following a favorable response to castration, the alkaline phosphatase may rise temporarily, signifying further osteoblastic response. There is usually a descent to lower levels when osteoblastic activity declines This does not necessarily indicate reactivation of the disease but is frequently an indication of the quiescent status of the disease following a period of bone repair These alterations in acid and alkaline phosphatase are often seen before clinical evidence of regression.

(*b*) Objective effects. Following the early effects in objective regression of the primary tumor, lymph node metastases, relief of urinary obstruction, cessation of hematuria, and a favorable response of osseous metastases may occur. Coincidental with these beneficial effects, there is usually weight gain, renewed vigor, and an increase in the erythrocyte count. Frequently, these patients with advanced disease are able to return to normal activities.

(*c*) Incidence and duration of effect An initial beneficial effect may be obtained in up to 75 per cent in any adequate series of patients with ad- [illegible] periods [illegible] 2, 84, [illegible] main [illegible] s not uncommon to observe new metastatic lesions while others are [illegible] The

this Committee have been published (123, 124) and another will appear shortly. These reports include the indications and possible effects of androgens as well as estrogens, indications for treatment, and the recommended dosages of the various compounds employed in the treatment of advanced breast cancer.

Effects of estrogen therapy.—(*a*) Objective. The most obvious effects of estrogens are on the soft tissue lesions of breast cancer in which responses occur with greater frequency and are better defined than those seen after androgen therapy. Ulcerations may heal, and gross masses, lymph node, pulmonary and hepatic metastases may considerably diminish in extent. In some instances, the lesions become barely detectable. Palpable masses frequently assume a fibrotic resilient character, even without significant reduction in size (43 to 46). Of especial significance is the fact that osseous lesions in postmenopausal women may calcify in essentially the same order of frequency as that seen with androgen therapy in women in any period of life (122, 125). Estrogens may likewise exert a favorable effect on advanced breast cancer in the male when employed either as a primary therapeutic agent or if reactivation of the disease follows initial response after orchiectomy (65)

(*b*) Systemic and general effect. Systemic improvement usually accompanies the objective favorable effects. The subjective and systemic responses are similar to those seen with androgen therapy but do not occur as frequently or as rapidly. However, in contrast to androgens, there is less discrepancy between the subjective and objective responses to estrogen therapy (122, 123, 124).

Estrogens are primarily indicated in the treatment of advanced primary breast cancer and its distant deposits in postmenopausal women, regardless of the chronologic age of the individual Recent data indicate that the effects of estrogen therapy are more nearly related to the menopausal status of the individual (122) The large percentage of patients who derive benefit are at least five years past the menopause or over 60 years of age. Acceleration of the disease may occur in premenopausal women, while in the recent menopausal group, variable responses ranging from acceleration to remissions may be observed. With these limitations, estrogens may favorably influence every manifestation of breast cancer.

Bladder cancer.—Estrogens have been tried as a method of therapy in advanced bladder cancer on the thesis that the bladder and prostate gland are of similar embryologic origin. Beneficial clinical improvement has been noted in a few patients [illegible]

disappeared It has also been stated that low-grade tumors show cytologic changes identical with those seen in cancer of the prostate gland treated with estrogenic therapy, while the more anaplastic tumors do not show any change. These observations need further investigation

would be removed with a possible favorable effect. Two patients died within a short period of time from adrenal insufficiency. The third was maintained for over 100 days with supportive therapy. There was little effect on the carcinoma.

ESTROGENS

Prostatic cancer.—The work of Huggins and his colleagues (67 to 70), Herbst (102), Dean & Twombly (47b), and others also indicated that estrogenic hormones might inhibit the effects of androgens on prostatic carcinoma. Clinically and metabolically, the effects are indistinguishable from those obtained by castration (93, 103 to 107). A latent period before responses are noted is usually longer than that seen after castration but usually occurs within a few weeks Nesbit & Baum (96) have recently analyzed the collective experiences of a number of clinics submitted to them in regard to the relative effectiveness of orchiectomy, estrogens, and a combination of these two forms of treatment. From these data, they have concluded that

> the present survey has demonstrated conclusively that patients with prostatic cancer who respond favorably to castration and/or estrogen therapy live more comfortably and longer than patients not treated by these methods. Patients who fail to show any response to treatment have survival rates that are identical to those of persons in the untreated control group
>
> Five-year control of prostatic cancer is most effectively obtained by the combined employment of orchiectomy and diethylstilbestrol in patients who are free from metastases. When metastases are present orchiectomy is significantly more effective than diethylstilbestrol, the combination of diethylstilbestrol and orchiectomy does not appear to offer any advantage over orchiectomy alone in this group of patients
>
> The maximum benefit is best achieved by the institution of treatment as soon as the diagnosis is established
>
> There appears to be no advantage of one form of therapy over the other when used in the treatment of relapse. The symptomatic improvement that occurs in some instances might well be due to improved nutrition and nursing care rather than a remission of carcinogenic activity.

Breast cancer.—Although earlier studies suggested that estrogens might be involved primarily in the causation and development of breast cancer, later experiments questioned the validity of this assumption (43 to 45, 108, 109). These latter data suggested that under some circumstances estrogens might have an inhibiting effect on an established breast cancer Hence, this possibility was further explored, and as a result, it has now been established that there is considerable variability in the response of breast cancer to estrogens and that under certain circumstances, there is retardation of growth or even regression of the lesions Early reports on this latter aspect by a number of investigators were followed by intensive studies in this direction (110 to 122) The English observers were particularly active in this regard. To a great extent, studies in this country were initiated by the establishment of a Subcommittee on Steroids and Cancer of the Therapeutic Trials Committee of the American Medical Association. Several reports of

metastases and symptoms referable to this manifestation of the disease. Osteolytic metastases from breast cancer calcify or appear to re-ossify in from one-fifth to one-fourth of the patients after androgen therapy, in women of any age. In some instances, as the original lesions apparently improve, new progressive osteolytic lesions are noted. Under other circumstances, rapid progression of existing osseous lesions may occur, especially if the patient is confined to bed Regressions of soft tissue lesions are less obvious but are seen more frequently in women in the premenopausal and recent menopausal eras than in later life.

(*b*) Systemic effects Symptomatic improvement, consisting of pain relief, increase in appetite and weight, and rehabilitation, is seen in a high percentage of patients, particularly those with osseous metastases There is considerable discrepancy between the subjective and objective improvement in any series of patients in that the former is very significantly higher. Actually, it is not unusual to observe continued progression or apparent acceleration of the disease in spite of excellent symptomatic relief. Coincidental with other beneficial effects, there may be an improvement in an existing anemia secondary to bone marrow involvement Symptomatic improvement, seen so frequently in patients with advanced mammary cancer, has been attributed to the metabolic capacities of the androgens

(*c*) Duration of effect The duration of favorable responses is variable, but in the majority of patients, recrudescence of the signs and symptoms appears within a year A number of patients, however, have experienced a steady, striking benefit for several years. In premenopausal women, castration is generally more efficacious than androgen therapy, presumably due to a more complete suppression of ovarian function. Thus, androgens may be utilized as palliative agents for advanced breast cancer in women at any stage of life. The effectiveness, however, is variable and is dependent upon the site of the lesions and to a limited extent upon the age of the patient.

Prostatic cancer.—Huggins & Hodges in 1941 (69) administered other doses of androgens for short periods to three patients with metastatic prostatic cancer. They found a rise in the serum acid phosphatase levels after androgen injection and concluded that the cancer was activated. Aub, Tibbetts & Nathanson in 1947 (152) reported on a patient who had received moderately large doses of testosterone propionate following reactivation of a prostatic carcinoma after an initial beneficial effect from estrogenic hormone. There was a marked increase in the acid phosphatase levels, and an increase in symptoms was seen after the administration of the androgen. This study was based on the premise that the administration of androgens might suppress the endogenous production of the similar hormones from the adrenal gland or testes through inhibition of the luteinizing or other hormones of the pituitary gland The patient appeared to improve after cessation of therapy but could not be followed for a long period because he sustained a cerebral injury which necessitated cessation of the investigation Munger also administered androgens with apparently favorable effects to several patients

Other tumors.—Three cases of chorioepithelioma, one of the testicle and two cases in females with pulmonary metastases, have been reported to respond favorably to estrogen therapy (127 to 129). As noted above, regarding sex differences in certain cancers, estrogen therapy has also been given to males with cancers of the lung and gastrointestinal tract. No definite effects have been obtained to date.

Androgens

Breast cancer.—Experiments in animals and observations in man implicating estrogens as possible causative factors in the development and growth of breast cancer led to studies of the effects of androgens on breast cancer in mice and the human being Nathanson & Andervont (130), Lacassagne & Raynaud (131) and others since have demonstrated that testosterone, administered under proper conditions, will partially inhibit the appearance of mammary cancer in a highly susceptible strain of mice. This presumably is brought about by a direct antagonism to the estrogens or by inhibition of pituitary activity. Androgens, however, have no effect on the tumor, once it develops in the mouse. Early observations by Loeser (132), Ulrich (133), and later Fels (134) indicated that androgens might have a favorable effect on established breast cancer. Although the number of cases was few and in some instances there were complicating factors, intensive investigation in this direction was indicated. Farrow & Woodard (135), in short term experiments using moderate doses of testosterone propionate, occasionally noticed symptomatic improvement but no definite effect on the primary tumor or the various manifestations of breast cancer. Actually, in other instances the patients appeared to fare badly. In these cases, the ill effects were ascribed to hypercalcemia when osseous metastases were present. Adair & Herrmann, using larger dosages over a longer period of time, reported definite and objective beneficial responses in 4 of 11 patients with advanced breast cancer (136). Consequently, in recent years a large number of observations have been made on the effect of androgens on curable and advanced breast cancer (137 to 148). Many of these studies were sponsored by the Subcommittee on Steroids and Cancer of the American Medical Association and are contained in the reports referred to above. Prudente has used androgens prophylactically after radical mastectomy in an attempt to prevent recurrence and increase the survival rate (149, 150) He reports increased survival rates in patients with axillary lymph node involvement, and thus far, there are no comparable series reported which have been treated in this fashion Adair has implanted testosterone pellets at the time of radical mastectomy in over 200 patients, but the time interval is too short as yet for critical analysis (151). Thus, information on this point is limited The effectiveness of androgen therapy in certain patients with advanced breast cancer is now well established. The effects are limited both as to site of response and duration.

Effects of androgen therapy.—(*a*) Objective. Androgens appear to be most efficacious in breast cancer in the production of favorable effects in osseous

with an elevated acid phosphatase did not respond, and in no instance was there a beneficial effect noted in patients in whom the serum acid phosphatase level was within normal limits at the onset of progesterone therapy. It has been theorized that progesterone inhibits the luteinizing hormone or a similar agent of the anterior pituitary gland which presumably is responsible for the production of androgens in the testes and the adrenal glands Thus, progesterone may suppress the endogenous production of androgens without an adverse direct effect on the tumor itself. Observations in our laboratory are in essential agreement with this point of view.

Types and dosage of hormone.—This subject has been purposely avoided. Various estrogens, androgens, adrenal cortical compounds, pituitary tropic hormones, and allied compounds have been tested for an effect on neoplastic diseases The optimum dosage and duration of the known effective compounds have not been determined conclusively. Newer compounds designed to incorporate the desirable features without the sometimes deleterious and undesirable side effects of the original preparations are now the subject of rigid testing Several reports have appeared suggesting that such preparations may be potentially effective in the treatment of neoplastic disease. It is too early to venture an opinion on these compounds. It is hoped, however, that studies in this direction will be continued and that more effective steroids and allied compounds will be forthcoming in the control of neoplastic diseases.

CONCLUSION

In recent months, a vast amount of work, both clinical and experimental, has been done with ACTH and cortisone in order to determine, if possible, their effect on various diseases This article surveys clinical and experimental observations of the effect of these drugs on neoplastic growth and mentions certain conclusions which seem tentatively justified by present knowledge. Neither ACTH nor cortisone appear to exert any certain influence on carcinoma or sarcoma per se They do not, on the whole, evoke beneficial responses in myelogenous and monocytic leukemia. In the lymphocytic series of tumors, they do not produce uniformly predictable changes. For example, in Hodgkin's disease, in which results are not outstandingly good, certain patients seem to derive real but temporary benefit from adrenocortical preparations, while others merely become afebrile and subjectively more comfortable. Lymphatic leukemia responds irregularly to administration of ACTH and cortisone, any ensuing improvement being temporary. For certain patients with multiple myeloma, these drugs bring dramatic improvement, while for others their effect is negligible. From such facts, it seems suitable to conclude that ACTH and cortisone affect the organism as a whole more than they inhibit tumor growth, although they do appear to inhibit normal growth They can, therefore, be classed as agents which affect the environment of tumors more than the tumors themselves There is some evidence that tumor growth is sometimes inhibited, but the irregularity of

with prostatic cancer who had become refractory to estrogen therapy (153) He postulated that androgens, under these circumstances, might prove beneficial since it was possible that the persistent cancer cells developed in an environment subject to estrogenic influence. Recently, Brendler *et al.* (154) treated three cases with testosterone propionate in moderately large doses in periods up to three months. Two of the patients had extensive secondary involvement of bone; both showed evidence of considerable improvement during the period of hormonal administration. Bone pain was considerably lessened in one of the two patients who had this complaint.

Cancer of the female genital organs.—Androgens have been used in the treatment of advanced cancer of the cervix, endometrium, and ovaries Some patients showed subjective improvement, presumably from metabolic effects of the hormone. Except in a few cases in which the effects appeared to be equivocal, there was no evidence of an objective improvement (155 to 158).

Other tumors—Testosterone propionate has been used in the treatment of a few cases of osteogenic sarcoma of the osteolytic type without any obvious effect on the tumor itself (61). Testosterone has also been used in patients with other types of cancer, but here, too, no objective effects could be demonstrated although the patients in some instances had occasional relief of pain and other favorable general subjective responses This has been attributed to the metabolic effects of the hormone

Progesterone

Cancer of the cervix and endometrium.—Recently, regressions of a number of cases of cancer of the cervix following intensive progesterone therapy have been reported (159) These effects have occurred usually within one month after the initiation of treatment. These observations are extremely interesting and should be an impetus for intensive investigation. Progesterone has also been tried in cancer of the endometrium, but to date, no definitely favorable effects have been recorded

Breast cancer—Attempts to influence breast cancer by progesterone have been made on a small series of cases (61, 159, 160). In a few patients, there was a suggestion of a beneficial response indicating further trials with this hormone In a few instances, there appeared to be an acceleration of the disease after progesterone administration

Prostatic cancer.—The use of progesterone in prostatic cancer appears promising Gutierrez reported that renewed regression with shrinking and softening of the prostate gland may be achieved by the administration of progesterone, even after reactivation of the disease following transitory improvement with castration or estrogen therapy (98). Trunnell *et al.* report similar results in untreated patients and those who relapsed after initial therapy with estrogens or castration (161, 162) Of the patients responding, all had an elevated serum acid phosphatase which decreased to constant lower levels at about the third week of therapy. However, other patients

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the effect indicates that further work is needed to elucidate the reaction

There is now indisputable evidence that the course and character of some cancers may be retarded by the administration or deprivation of sex hormones. Hormones have the greatest value when the disease is beyond the control of established procedures. As further exploration continues, it becomes progressively more obvious that, so far, endocrine therapy singularly affects only certain groups of tumors. This implies a unique specificity which is related to the intrinsic characteristic of the particular cells influenced rather than an effect on neoplastic growth in general.

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DISEASES OF BONES AND JOINTS

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In preparation of a review of diseases of bones and joints, the reviewer must necessarily limit himself in some manner so that the contribution of the review will be fairly complete in the portions of the field which are reviewed. Accordingly, this review will cover only the subjects of rheumatoid arthritis and gout.[1]

RHEUMATOID ARTHRITIS

In the past several years the number of articles appearing on the various aspects of rheumatoid arthritis is huge and the subject matter often repetitious. Aside from the hormonal studies begun by Hench and his group on the use of cortisone and adrenocorticotropic hormone (ACTH) in the alteration of the rheumatic and other collagen diseases little has been done but to accumulate a host of negative results Several new laboratory methods have been used but in final summary, they have not contributed much to the picture except to increase the confusion. There is no single clinical laboratory test which can with certainty diagnose rheumatoid arthritis The host of available tests resemble a chemical, hematological, and histological jungle through which the clinician must forge his way toward diagnosis of an individual case

Laboratory and clinical aspects.—Sokoloff *et al.* (1) studied the technique of muscle biopsy in 202 cases of rheumatoid arthritis and other rheumatic diseases including rheumatic fever, degenerative joint disease, gout, and infectious arthritis, as well as in healthy individuals They described infiltrations of lymphocytes in small nodules in the muscles of 56 per cent of the patients with rheumatoid arthritis, but such lesions were also present in 3 of 13 healthy volunteers, 4 of 10 with ankylosing spondylitis, 7 of 21 with rheumatic fever, 3 of 10 with joint tuberculosis, and 4 of 19 with osteo- [illegible] s, and [illegible], with [illegible] cent. They concluded that the use of muscle biopsy was of little diagnostic value in rheumatoid arthritis.

Collins *et al* (2) discussed the significance of pathological tests in rheumatoid disease. Reviewing the work of his group and others, he found that a high cell count in joint fluid, i.e , 20,000 cells per cu mm. and over, differentiated rheumatoid arthritis from osteoarthritis where the average count was 2,000 cells per cu. mm. The presence of blood pigment in the joint fluid was characteristic of traumatic effusion They felt that a positive diagnosis of

[1] This review covers the years 1949 and 1950 with inclusion of significant contributions of the recent past when necessary for emphasis

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normal limits. Woodmansey & Wilson (6) described a method for measuring plasma viscosity and felt that the study of the plasma viscosity gave a more accurate figure than the ESR for estimating the activity of rheumatoid arthritis They noted.

proteins may be broadly divided into two classes, fibrillar and globular. These are named according to whether the molecule exists as a long chain, albeit with foldings and side groups, or whether it has a more or less spherical form. It is considered that the former type presents greater frictional contacts in solution, and that it therefore leads to increased viscosity. It is thus easy to understand how a qualitative change in plasma proteins brought about by disease processes could influence viscosity.

Desmarais *et al.* (7) showed that among 56 cases of typical idiopathic rheumatoid arthritis, 34 (60.7 per cent) showed round cell foci and thickening of the walls of the blood vessels. These changes appeared to be present both in active cases and in those which appeared to be "burned out." Among those cases of less than six months duration, no typical rheumatoid changes were found In those examined within three years, seven years, and from eight years onward, the chances of finding the lesions appeared to be 47 per cent, 60 per cent, and 82 per cent, respectively. Seventeen of the 34 positive cases showed positive pathological findings elsewhere in the synovia, skin, or subcutaneous nodules, and four cases with negative muscle biopsies showed typical histological change in other mesodermal tissue. Of four cases of rheumatoid arthritis with psoriasis, only one gave a positive muscle biopsy. Among 17 cases of ankylosing spondylitis, all biopsies were negative. The muscle biopsies of 15 nonrheumatic controls were also negative

Wallis (8) studied the serum proteins in rheumatoid arthritis. His electrophoretic analysis of samples from four patients showed that there was an increase in the alpha (inflammatory) and the gamma (antibody response) components, chiefly the latter. Three of the four patients showed a T-component not previously reported in rheumatoid arthritis serum Examination of samples from 10 patients utilizing rabbit antihuman γ-globulin serum showed greatly increased γ-globulin values which averaged more than twice the normal content of this component when examined by immunological methods He felt that his data indicated that hyperglobulinemia of active rheumatoid arthritis is the result of the combined effect of inflammation, tissue destruction, and immunization, the latter being the major contributor in all but the early stages of the disease He felt that the "hyperimmunity" of severe rheumatoid arthritis is due to an antigen which is not necessarily of infectious origin but which could be derived from the patient's own tissues and that the antibodies serve no useful purpose, moreover, for the sake of this excessive antibody production, the patient apparently sacrifices his plasma albumin, his hemoglobin, and his general tissue nutrition

Lush *et al* (9) discussed the total and differential protein levels of the blood and cerebrospinal fluid in rheumatoid arthritis In their study, they did not find it possible to correlate the results with clinical findings, and it

rheumatoid arthritis could be made on synovial biopsy if the following five features were present (*a*) hyperplasia of the synovial membrane and villi, (*b*) hyperplasia of lining cells, (*c*) massive lymphocyte or plasma cell infiltration with focal collections, (*d*) inflammatory hyperemia and edema, and (*e*) absence of other specific histological features. In discussing the use of plasma viscosity (relative to water) in rheumatic diseases in 365 observations on 286 consecutive patients with rheumatoid arthritis, they reported that 41 were within the normal range, as compared with 38 out of 40 healthy persons. The erythrocyte sedimentation rate (ESR) in the same cases was within the normal range in 34 cases, as compared with 39 out of 40 controls. They concluded that the ESR and the plasma viscosity showed two different aspects of plasma abnormality, the sedimentation rate being influenced mainly by fibrinogen and the viscosity mainly by globulin. Among patients with ankylosing spondylitis, only 3 out of 34 patients showed values within the normal range, but with a high ESR; the reverse was seen in one instance only. Among their cases with osteoarthritis, 24 of 42 with osteoarthritis had a raised ESR, and 22 of 42 showed a raised viscosity. Among those with fibrositis, only 1 of 32 showed increased viscosity, and they concluded that plasma viscosity determinations were important aids but were supplementary to and did not replace the value of the determinations of the ESR.

Plasma viscosity in the rheumatic diseases was also studied by Cowan & Harkness (3) who concluded that it increased with progressive disease in rheumatoid arthritis and decreased with improvement. The increase was roughly proportional to the severity of the disease process. In osteoarthritis, on the other hand, the plasma viscosity values tended toward normal. This seemed to indicate that osteoarthritis was more of a local disorder which produced little or no systemic reaction. Patients with fibrositis and myositis presented normal viscosity values Lawrence (4) described a method for studying the viscosity of the plasma He felt that the results of his study indicated that the changes in disease depend more on the stage of the disease than the nature of the process. His method makes possible the determination of differential plasma viscosity. A comparison of the differential plasma viscosity with the ESR and with simple plasma viscosity indicated that the first was a more sensitive indicator of pathological plasma protein change than either of the other two and that the ESR is the least reliable.

Houston (5) studied the plasma viscosity in pulmonary tuberculosis and rheumatic diseases. His studies showed that among 289 patients with pulmonary tuberculosis, plasma viscosity increased with a spread of the disease. In more than 750 tests on rheumatic disease, it was found that in every case in which plasma viscosity was raised to an abnormal level, an underlying organic cause was found. In rheumatic fever, the viscosity increased as the disease progressed and decreased during recovery. In rheumatoid arthritis, however, the increased viscosity was roughly in proportion to the severity of the pathological processes and to the systemic reaction. In nonarticular rheumatism (fibrositis), the viscosity values remained within

the specific agglutination of sheep-cells, did not show a similar effect on the specific hemolysis of the cells

Pike and co-workers (11) also showed the interesting fact that the rheumatoid arthritis serum not only agglutinated sheep-cells sensitized with rabbit anti-sheep-cell serum, but also agglutinated sheep-cells sensitized with rabbit anti-goat-cell serum and with rabbit anti-guinea-pig kidney serum Sheep-cells sensitized with the serum from patients with infectious mononucleosis and normal persons were agglutinated to about the same degree as unsensitized cells. Adsorption of agglutinins for autoclaved group "A" streptococci from rheumatoid arthritis serum did not affect the titer of the serum for sensitized sheep-cells It appeared that the property of amplifying specific agglutination was present to some extent in many human and animal sera and that the marked activity of serum in rheumatoid arthritis may have simply represented an increase of this normal property.

Brown *et al.* (12) found that the sheep erythrocyte agglutination test was positive in 55 per cent of 62 patients with rheumatoid arthritis and in 30 per cent of 20 patients with inactive rheumatoid arthritis They found a close but not exact correlation with *Streptococcus* agglutinin titers The incidence of elevated differential titers increased as the duration of the disease increased. There was no correlation in the presence of a high titer and subcutaneous nodules. In the nonrheumatoid control group of 83 sera, only one had a differential titer of 16. All others were below that value Rose, Ragan, *et al.* (13), in their initial study of this phenomenon, noted that the high differential titers were found to occur almost solely in serum of patients suffering from active rheumatoid arthritis. These workers were responsible for the first observation of this phenomenon.

Sulkin (14) has studied the specificity of the reaction and found that in cases of mild severity the test was of little diagnostic value and that, as in the work of others, the tests seemed to reflect the clinical severity of the disease Their figures showed that sera from 88 individuals with a variety of other conditions and from 18 normals showed titers of less than 16, whereas when serum specimens from 42 individuals with rheumatoid arthritis were examined, serum from 17 of these showed differential agglutination titers of 16 or greater In 24 active cases of mild and moderate severity and in one inactive case of long duration, a differential agglutination titer of less than 16 was obtained. Svartz (15) noted that the use of ACTH was not effective in reducing the agglutinating factor against sensitized sheep-cells in cases of rheumatoid arthritis She also noted that a raw extract prepared from suprarenal capsules of guinea pigs and other animals checked the agglutination reaction, unlike the situation where kidney extract was used

Granirer (16) studied the prothrombin time in rheumatoid arthritis among 15 patients treated for one year with therapeutic doses of goldthioglucose and crude liver extract. Among these patients, there was no increase in the prothrombin time. Wallraff (17) studied the tyrosine excretion in rheumatoid arthritics and normals and noted that tyrosine, which is

was concluded that the estimation of the cerebrospinal fluid protein is of no clinical importance. The serum globulin and the globulin/albumin ratio have been found to be significantly increased. They found that the mean total cerebrospinal fluid protein levels in both sexes were similar and above the normal mean. The mean cerebrospinal fluid globulin was raised in both sexes but to a significant degree only in the male The mean cerebrospinal fluid albumin was normal in the male and significantly raised in the female The authors felt that one possible explanation for the protein changes could be that there was some degree of liver dysfunction or that the possible source of excess globulin was from lymphocytes and was an antibody response to an unknown causative antigen.

Swanson (10) discussed the value of repeated colloidal gold tests (serum) in rheumatoid arthritis and concluded that there were three types of results obtained: (*a*) those always positive, (*b*) those always negative, and (*c*) those which were sometimes one and sometimes the other, and that a single colloidal gold determination was of no value in assessing the clinical activity of the disease. Repeated tests were of value in estimating the progress and prognosis Generally speaking, results tending to become less positive indicated a good prognosis Repeatedly, strong tests indicated a bad prognosis, and those which were positive and sometimes negative probably indicated a still undecided outcome. The disease had to be of at least six months duration before the tests became positive. They found no relation between the results of the tests and the age or sex of the patients, the degree of arthritic change, or of gold therapy given. There was no relation between the results of the colloidal gold test and the blood sedimentation rate The explanation was offered that when persistently negative results were seen in clinically active cases, the reaction was being masked by one or more of the other protein fractions which were also elevated.

There have been several studies of the differential sheep cell agglutination test in rheumatoid arthritis. Pike *et al.* (11) studied the factors affecting the agglutination of sensitized sheep erythrocytes in rheumatoid arthritis serum, and they described a method for demonstrating the effect of serum from arthritis patients on the agglutination of sheep erythrocytes by small amounts of rabbit anti-sheep cell serum and the influence of certain factors in the reaction. The degree of agglutination appeared to be dependent on the concentration of anti-sheep cell antibody which should be standardized for the test on a basis of its agglutinating rather than its hemolytic capacity. The property of rheumatoid arthritis serum affecting the agglutination of sensitized sheep-cells was found to be stable on storage for several months The capacity of rheumatoid arthritis serum to influence the agglutinability ... content of sheep

with lipoid solvents failed to destroy its capacity to agglutinate the sensitized sheep-cells. The rheumatoid arthritis serum, which markedly increased

the specific agglutination of sheep-cells, did not show a similar effect on the specific hemolysis of the cells.

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bound so as to be microbiologically unavailable without hydrolysis, is elevated in the rheumatoid arthritic urine. They concluded that the difference may be due to differences in assimilation of protein or to a metabolic abnormality.

Darley (18) considered the data from 74 patients in whom the diagnosis of chronic brucellosis was probable. Among those patients, the most frequent symptoms encountered were fatigue, muscle and joint aches and pains, nonmigrainous headache, digestive complaints, and low grade fever. The absence of physical abnormalities was conspicuous in this group The incidence of positive agglutination reactions was significantly high, but the author felt that after a critical study, every possible explanation for symptoms must carefully be considered before the diagnosis of chronic brucellosis is justifiable. This work is worthy of note in view of the frequency with which brucellosis is falsely attributed to be the cause of rheumatoid arthritis

Rimington (19) reviewed the studies of synovial fluid mucin, noted its physical and chemical characteristics, and emphasized that its abundance appears to be influenced by hormonal changes It is possible that the loss of elasticity of the subcutaneous tissue among the older age groups has a relationship with the diminution of the quantity of mucin.

Morrison (20) discussed the neuromuscular system in rheumatoid arthritis in regard to electromyographic and histologic observations. Their conclusion was that the direct involvement of the neuromuscular system by the disease process seemed highly likely and might explain the neurologic signs and symptoms so prominent in the disease, including muscle weakness and atrophy. In 26 out of 31 cases, lesions were found in the peripheral nerves, and in 8 of 14 cases, lesions were found in muscles similar to those observed in other studies The presence of involuntary skeletal muscle activity was noted in 50 per cent of 34 patients with rheumatoid arthritis A similar pattern was observed in patients with anterior poliomyelitis, peripheral nerve injuries, infective polyneuritis, and spinal cord lesions This spontaneous skeletal muscle activity may be explainable on the basis of pathologic lesions of the lower motor neuron.

Wallis (21) noted that it is possible that rheumatoid arthritis results from over-stimulation of the constrictors of the peripheral arterioles to the extent that they enter a state, not of exhaustion and relaxation, but of diminished responsiveness and increased fatigability. He felt that tissue-fixed antibodies might contribute to vasoconstrictor fatigability by offering resistance to the action of vasoconstrictor muscle He also hypothecated that vasoconstrictor overstimulation and fatigability might lead to a metabolic derangement in the synovial cells with the breakdown of protoplasm into a chemical irritant, the molecules of which are too large to enter the capillaries, and, therefore, in the absence of papillary lymphatics, cannot be dispersed by the local application of heat

Rosenberg *et al.* (22) studied the findings at necropsy of the hearts of patients with rheumatoid arthritis One hundred fourteen patients with

rheumatoid arthritis of the peripheral joints and 33 having rheumatoid spondylitis were examined in detail to determine the incidence of major and minor cardiac abnormalities Similar studies were conducted concurrently on 100 nonarthritic persons most of whom were well and a few of whom were undergoing treatment for injuries. Auscultatory, roentgenographic, sphygomanometric, and electrocardiographic studies of these two groups of patients disclosed that the incidence of rheumatic heart disease judged on clinical evidence in the arthritic groups was not significantly higher than the incidence of this condition among controls. This pointed out the apparent difference in the incidence of the complication of rheumatic heart disease in the living and dead patients with rheumatoid arthritis.

Schwartz & Steinbrocker (23) attempted without success the production of rheumatic subcutaneous nodules in 39 patients with rheumatoid arthritis, in 18 patients with rheumatic fever, and in 15 normal controls by injection of whole blood over the olecranon and applying friction to the injected area, by injecting a solution of trypsin over the olecranon, and by injecting joint fluid from a patient with active rheumatoid arthritis over the olecranon and applying friction.

Lucchesi (24) studied the significance of subcutaneous nodules in rheumatoid arthritis and found that their presence does not indicate an unfavorable outlook, cardiac involvement, or enhanced activity or intensity of the disease and that their presence constituted no obstacle to treatment. This is in contradistinction to the prognostic importance of subcutaneous nodules in rheumatic fever where their presence usually indicated a more grave prognosis Kersley *et al.* (25) in a comprehensive study of the rheumatic nodule reported on nodule examination from 27 cases as a result of which the nodules were classified into five main groups (*a*) Two cases of gout showed nodules, and in one of these in addition to uric acid in the nodules, cholesterol was demonstrated (*b*) Eight cases were typical rheumatoid arthritis Among these, two had some symptoms of hypothyroidism; the excised nodules contained cholesterol deposits, both intra- and extracellular, and "foam cells" were seen in some fields. Nodules from three cases of atypical rheumatoid arthritis with features suggestive of gout were shown to have the structure of rheumatoid arthritis nodules. In one patient who had had rheumatoid arthritis actively but had no active signs of the disease, the excised nodules showed the typical rheumatoid changes (*c*) There was a case of rheumatic fever in which a nodule was excised and showed the changes typical of that condition (*d*) Four cases were of fibrositis In these, three of the cases showed the structure of lipomata, but the fourth showed some areas of lymphocytic infiltration suggestive of the lesions which are found in the muscle, nerve, and joint tissues in rheumatoid arthritis. (*e*) Four cases were described as fibrous nodules on the fingers and hands but with no clinical or pathological signs of rheumatic disease

Copeman (26) discussed fibrofatty tissue and its relation to certain rheumatic syndromes He cautioned against terming pathological changes

bound so as to be microbiologically unavailable without hydrolysis, is elevated in the rheumatoid arthritic urine. They concluded that the difference may be due to differences in assimilation of protein or to a metabolic abnormality.

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frequently, they were in relation to a blood vessel. In the myelin sheaths of axons, pathological changes showed. Such changes were also seen in the "group" diseases including dermatositis, lupus erythematosus, and rheumatic fever.

Lush *et al.* (28) reported a case of rheumatoid arthritis and amyloid disease. They pointed out that amyloid tissue, like mucin, is a glycoprotein, and it may be that this relationship is worthy of further investigation since there is some evidence that mucolysis occurs in the joints in rheumatoid arthritis. The incidence of amyloidosis in connection with rheumatic disease has not been studied adequately. Kersley (29) reported the spontaneous rupture of muscle as the complication of rheumatoid arthritis. This rupture was unassociated with any sudden strain or unaccustomed exercise and was thought to be secondary to rheumatoid changes.

Davidson (30) discussed the question of focal infection in rheumatoid arthritis using 100 cases of rheumatoid arthritis and 100 suitably selected controls. Actual or potential foci were found in 44 per cent of cases of rheumatoid arthritis and in 43 per cent of controls Eight patients in the rheumatoid group had a history of infection in the upper respiratory tract within three months of the onset of arthritis No significant information was obtained from study of the material expressed from tonsillar crypts nor from bacteriological examination of the tonsils and pharynx which was of value in differentiating cases of arthritis from the controls Davidson felt, on the basis of his examination, that infections of the ear, nose, and throat did not play an important part in the etiology of the disease. He did not discuss the possibility that in rheumatoid arthritis, an altered reactivity to common pathogenic organisms in the infected foci might be of importance. Apparently, this whole question deserves reinvestigation regarding both the incidence of infected foci and the degree of reactivity of the rheumatoid and control groups to various pathogens isolated from such foci

Etiological concepts.—Wallis (31) advanced a theory of the pathogenesis of rheumatoid arthritis in which he states that two prerequisites for the development of rheumatoid arthritis are "to be eligible to acquire this disease a person must be endowed with a potentially high superficial peripheral vascular tone, and to become involved in the disease process the tissue must be [illegible]

ther [illegible]

of the [illegible]

tant substance Haydu & Wolfson (32) noted that rheumatoid arthritics had a diminished glucose tolerance as compared with chronic patients under the same conditions. Further, the rheumatoid patients did not show the same decrease in sugar tolerance when treated with insulin and glucose as did other chronic, nonrheumatic subjects Rheumatoid patients increased glucose tolerance when treated with insulin and *dl*-sodium lactate for five weeks. They showed a decrease in glucose tolerance when treated with insulin and citric acid of similar magnitude with those of nonarthritics

in fat as being caused by arthritis. He emphasized that in certain instances, the fat herniates through fibrous tissue into adjoining layers and can be extremely painful. He emphasized the importance of surgical removal of irreducible fat herniae and, to a similar extent, removal of localized areas of painful tissue in severe cases of panniculitis.

Bauer & Clark (27), reviewing the systemic manifestations of rheumatoid arthritis, emphasized that rheumatoid arthritis is a systemic disease and not solely a disease of joints In reviewing their anatomical material, they gave the following statistics. Skin lesions were present and resembled a variety of dermatological conditions. Psoriasis was present in 2 7 per cent of the first 300 patients studied. Altered pigmentation, erythemas, and purpuras were observed less frequently, but erythemas and purpuras were seen during exacerbation. Subcutaneous nodules were present in approximately 15 per cent, and in most cases, these could be distinguished from the subcutaneous nodules of rheumatic fever on histological examination on the basis of the marked proliferation and degeneration of the connective tissue generally predominating in the rheumatoid nodule. Iritis was the most common ocular lesion associated with rheumatoid arthritis, and the scleral nodule (scleromalacia perforans), although infrequent, was seen occasionally. On histological examination, it had the same appearance as the subcutaneous nodule Among 45 cases where necropsies were possible, extensive atherosclerosis of the aorta and the coronary arteries together with degenerative changes in the myocardium was the common finding. Pericarditis was present in 44 per cent, but in only 50 per cent was it associated with myocardial infarction or alteration suggesting rheumatic fever. There was focal myocarditis without definite histological evidence of rheumatic carditis in 15 per cent. Twenty per cent had some degree of valvulitis which had resulted in mitral stenosis in 14 per cent In only one of these could a definite diagnosis of rheumatic heart disease be made. An unidentified aortitis was observed in three cases. In one, there was an associated aortitis with pannus formation Two hearts showed pericardial nodules resembling histologically the subcutaneous nodules Inflammatory foci were demonstrable in tendons, bursae, and muscle Alterations of skeletal muscle were found in 50 per cent of cases. These alterations, consisting of collections of lymphocytes, plasma cells, and occasionally epithelioid cells located in both the perimysium and the endomysium, varied from definite nodular forms to small collections of lymphocytes and plasma cells usually in relation to a blood vessel. Such lesions were also seen in dermatomyositis, lupus erythematosus, and scleroderma Examination of the central nervous system in 44 patients showed no specific lesions of the brain or cord Alterations attributable to aging were, however, more common in the arthritics than the control group of the same age, particularly in the lateral projections of the anterior horn In 28 of 31 cases examined, inflammatory reactions were found in the peripheral nerves, chiefly in the nerve sheath in the perineurium They were similar in appearance and cellular composition to those seen in the skeletal muscles, and

rheumatoid arthritic condition He suggested that the inactivation of trypsin by a low oxidation-reduction potential or the reducing capacity of digest mixtures indicated an association of these results with such substances as cysteine in chronic rheumatic disorders and becomes allied with such therapeutic methods blocking the disulfhydryl groups of enzymes by heavy metals.

Kalbak (40) noted that the agglutination of hemolytic streptococci (group A) in serum from patients with rheumatoid arthritis was positive in about 80 per cent of 241 patients, whereas, among 900 control patients, it was positive in only a very low percentage. Gibson & Shiers (41) reported a control series of Cooke-Arneth polynuclear counts in rheumatoid arthritis and noted that there was no difference between the polynuclear counts of

support to the view that rheumatoid arthritis is the result of microorganismal infection. On the other hand, Boni (42) discussed the fall in serum iron and rise in serum copper level occurring in infections. He noted that serum iron levels were altered in patients with rheumatoid arthritis, and he considered such alterations to be indicative of an infective component in the etiology of the disease. The antistreptolysin titer was elevated in 23 per cent of the patients with rheumatoid arthritis. Sixty-five per cent of the cases showed positive agglutination for Group A streptococci, the result being negative in all cases of long (10 to 20 years) duration Bywaters (43) reported on a variant of rheumatoid arthritis characterized by recurrent digital pad nodules and palmar fasciitis closely resembling palindromic rheumatism. He reported three cases which were characterized by digital pad nodules, transient palmar contractures, and transient articular swellings. Biopsy material showed the nodules to be rheumatoid in type. Radiologically, changes in the juxta-articular bone were seen, atypical in one case and identical with rheumatoid arthritis in the others This entity is evidently quite rare, and the author compared and contrasted these cases to palindromic rheumatism, gout, and rheumatoid arthritis and concluded that they most nearly resembled palindromic rheumatism, although "pigeon-holing of sick men and women is a necessity to the clinician and his daily craft, but a hindrance in his pursuit of the truth."

Juvenile rheumatoid arthritis.—Pickard (44) discussed the status of rheumatoid arthritis in children using the records of 200 children suffering from this disease Essentially, he agreed with the idea that rheumatoid arthritis in children is self-limited, and he showed that prognostically the results were poorest in those showing involvement of the elbows, carpal joints, and wrists and were relatively good in those in which the ankles and knees were involved Amyloid degeneration of the liver and spleen was described. Evidence of cardiac disease was present in the severe cases. A persistent monoarticular form of rheumatoid arthritis in children is sometimes difficult to distinguish from tuberculosis Lockie & Norcross (45)

similarly treated. The fasting levels of blood glucose exhibited the same type of response as did the glucose tolerance curves. The authors felt that in rheumatoid arthritis, one is confronted with a great increase in enzymatic avidity and with an attendant disorganization of the adenosinetriphosphate (ATP) energy donor system and that the deficiency of the ATP system in rheumatoid arthritis is due to "an increased enzymatic activity, a continuous *increased effort*."

Dickson (33) indicated that more emphasis should be given to the study of altered physiology rather than altered pathology in the study of rheumatic disease. He felt that among the many causes assigned to rheumatoid arthritis, fatigue was common to all of them. Martin *et al.* (34) noted that patients with rheumatoid arthritis were often intolerant to cold because of incompetent vasoconstrictor response and that vasodilatation from heat was slow. Hench (35) discussed the potential reversibility of rheumatic disease. Pregnancy promotes a remission in rheumatoid arthritis in a high percentage of cases, although the application of female hormones did not result in the same fortuitous circumstance. Transfusions of blood from pregnant women, however, were followed by rapid improvement in the general condition of the patient. These results have been characterized as "satisfactory" rather than "dramatic" Jaundice, both spontaneous and induced by a variety of measures, was observed to promote a measure of improvement in the rheumatoid arthritis as long as it was present. He pointed out that gold therapy would only bring about striking remissions in 10 to 15 per cent of cases, whereas, jaundice or pregnancy would be followed by remission of the articular symptoms in 60 to 90 per cent of the cases

Parr discussed hand patterns in rheumatoid arthritis (36) in which he listed 15 types of hands commonly seen in diagnosis of rheumatoid arthritis and related the hand patterns to changes in ESR and to therapy. He made considerable point of the differentiation between the vasoconstrictive variety of rheumatoid arthritis and that characterized by periarticular thickening. The keen clinical observation in this analysis of hand patterns seems to be deserving of further study and elaboration. Jonsson (37) discussed rheumatological hand and finger symptoms and indicated "that knuckle pads and Dupuytren's contracture have similar histological changes"

Jarvinen (38) studied the interrelation of rheumatoid arthritis and diabetes mellitus among 1,008 rheumatoid arthritics and 766 diabetics and concluded that these diseases have no tendency to occur together or to avoid each other. In 13 cases in which the patients had both diseases, there was no evidence of mutual effect of the diseases upon each other, but in two cases of rheumatoid arthritis, the symptoms were aggravated with the onset of diabetes, and in one case of diabetes, the symptoms were aggravated with the onset of rheumatoid arthritis Coke (39) studied the serum antitryptase in chronic rheumatic disease and concluded that in a series of 200 patients with chronic rheumatic disease a quantitative relationship existed between the antitryptase level of the serum and the extended activity of the

the influence of pregnancy, viz., ankylosing spondylitis often became manifest for the first time during pregnancy, thus differing from rheumatoid arthritis of the peripheral joints where pregnancy usually induced temporary remission. In 8 per cent of their cases, there was a family history of the disease They noted that in some cases under their constant observation for many years, the clinical signs of the disease were present for several years before the development of changes in the x-ray appearance of the sacroiliac joints.

Treatment of Rheumatoid Arthritis

Steinbrocker and co-workers (54) have devised a therapeutic scoring system for rheumatoid arthritis which is a standardized method of appraising the results of treatment This method merits widespread acceptance since cases can be grouped numerically at regular intervals regarding the degree of therapeutic response. This method has much to recommend it to all clinical investigators who would standardize their evaluations of the proposed remedies for rheumatoid arthritis. In fact, it is surprising that editors now will accept articles which do not follow this or similar methods of evaluation.

Short & Bauer (55) reported the course of 250 unselected patients with rheumatoid arthritis who received simple medical and orthopedic measures and were under continuous observation for a period of 10 years In this group, over 50 per cent showed a definite degree of improvement when last seen. Fifteen per cent were in remission. In their group were patients with ankylosing spondylitis as well as patients with rheumatoid arthritis of the peripheral joints. Those with spondylitis showed improvement in 44 8 per cent, and those without spondylitis in 54 6 per cent Likewise, among those who were the worst, were 36 7 per cent with spondylitis and 33 6 per cent without spondylitis Patients improving were 58.4 per cent of males and 50 per cent of females and among the worst were 27.8 per cent of males and 37.8 per cent of females In segregating the patients according to age, they found that 61 6 per cent of patients under 40 years of age improved and 41.8 per cent of those over 40 improved Where the disease existed less than one year prior to observation and simple medical treatment, 73 9 per cent improved, whereas in those where the disease had existed over one year, 43.7 per cent improved Those whose presenting clinical picture was characterized by symmetrical joint involvement from the onset showed only 56 per cent improvement, and among those whose joint involvement became symmetrical after beginning asymmetrically, only 40 per cent improved Among those who were asymmetrical on admission, 82 per cent improved Among those with spondylitis, only 44.8 per cent improved. Among those with extensive joint involvement, only 19.4 per cent improved, whereas, among those with mild involvement, 70 5 per cent improved. The relapse rate was shown to be quite high Among a group of 84 cases which showed improvement within two years, 46.5 per cent showed later relapse. In the

studied 28 cases of juvenile rheumatoid arthritis over a period of 14 years Their results showed that death occurred in 7 per cent while the disease remained active in 10 per cent. Complete recovery occurred in 43 per cent, mild residual deformity in 21 per cent and moderate residual deformity in 11 per cent. Severe residual joint deformities occurred in 7 per cent. Françon (46) reported an example of chronic rheumatoid arthritis of the juvenile type with precocity of the secondary sexual characteristics.

Psoriasis with arthritis.—Wassmann (47) reported on association of rheumatoid arthritis and psoriasis statistically. In 10,000 medical patients, psoriasis of the skin was found in 4.3 per thousand, while among 1,000 patients with rheumatoid arthritis, psoriasis was found in 3 1 per cent. Klinck (48) reported the favorable use of injections of γ-globulin in patients with cutaneous psoriasis, although no such study in psoriatic arthritis was noted.

Ankylosing spondylitis (rheumatoid arthritis of the spine).—In recent years, clinical observation and more accurate reporting has resulted in the finding that there is a definite familial incidence of ankylosing spondylitis and that females are more commonly afflicted than was formerly recognized. Doubtless the faulty earlier data were based upon predominantly male military or industrial practice. Rogoff (49) studied the familial incidence of rheumatoid spondylitis and found that among the close relatives of 114 subjects with rheumatoid spondylitis, the familial incidence of this was found to be at least 9 per cent. Riecker *et al.* (50) reported on a family extending over four generations and composed of 87 persons, including in the second generation a sibship of 12 individuals ranging in age from 3.6 to 59 Verified ankylosing spondylitis was present in three persons in the second generation and in two of their five children in the third generation. Three of the five affected persons are females, and it is more than probable that in the first generation the female progenitor of the kindred also had the disease The individuals composing the fourth generation were still below the usual age of onset of the disease In this family, the disease appears to be transmitted as if due to a single autosomal dominant gene whose exact frequency of expression could not be specified. Fraser (51) reported the incidence of ankylosing spondylitis in sisters.

Desmarais (52) suggested that the simultaneous and directly opposite processes of osteoporosis on the one hand and sclerosis with abnormal calcification of the ligaments on the other are a cause of the frequent normal values of the serum phosphatase activity in ankylosing spondylitis Parr, White & Shipton (53) reported a series of 100 patients with ankylosing spondylitis among which 57 were males and 43 were females They emphasized that x-ray therapy, judiciously used, remains the chief therapeutic weapon and has changed the entire outlook for those with ankylosing spondylitis, but they suggested that in some instances, cup arthroplasty for associated involvement of the hip joints might be beneficial when the arthritis of the spine was stabilized. They also made an interesting observation regarding

hematocrit, and ESR. Those given plasma alone showed no improvement in these measurements Serum and plasma flocculation tests showed no correlation between protein abnormalities and test reactions. These 50 patients were reviewed after an interval of six months and compared with 50 patients who received no blood transfusions. Among those who received whole blood transfusions, the hematocrit level and the erythrocyte sedimentation rates were better than in the group not receiving blood. The arthritis was apparently not much affected by the transfusions, but the general condition of these patients was improved, and the method was considered to be a useful supporting measure deserving of wider use

Smith (59) reported on the use of *p*-aminobenzoic acid with sodium salicylate in treatment of rheumatoid arthritis. Symptoms of toxicity occurred in 69 patients using sodium salicylate but in none using the combination. Those taking the combination showed subjectively less pain than those given the sodium salicylate alone Apparently, using the combined therapy gave greater duration of relief of pain as well. Duthie & Swanson (60) reported on the use of *p*-aminosalicylic acid in the treatment of six cases of rheumatoid arthritis with no apparent therapeutic benefit. Toxic symptoms were noted in three of the six cases and treatment had to be discontinued. Varying degrees of hypoprothrombinemia were noted in all cases Meyer & Ragan (61) reported on the antirheumatic effect of sodium gentisate. They reported that sodium gentisate appeared to exert antirheumatic activity equal to or greater than that of salicylate No untoward effects were observed in patients given moderate doses The authors noted that the increased urinary excretion of glucuronic acid observed with sodium salicylate did not occur with the gentisate.

Blumencron & Borkenstein (62) reported on the intravenous use of the ethanolamine salt of salicylic acid (Solusal) They found that the intravenous administration was well tolerated by patients who could not tolerate the drug orally and that generally higher salicylate blood levels could be obtained than when using sodium salicylate Holtz (63) reported on the clinical use of salicylamide in rheumatic disease and concluded that its action was similar to that of acetylsalicylic acid and sodium salicylate Wegmann (64) reported that the use of salicylamide produced a good, moderate, and slight effect, respectively, in 10, 5, and 6 of 21 patients with degenerative joint disease, and in 9, 3, and 2 of 14 with rheumatoid arthritis. Stettbacher (65) reported on severe essential thrombopenia and severe anemia developing in a 48-year-old woman who had taken 144 gm. of salicylamide within three months The patient recovered with blood transfusions

Svartz reported on the use of salicylazosulfapyridine in the treatment of rheumatoid arthritis (66) She emphasized that this drug, like all acid-azo compounds, showed a marked affinity for connective tissue, especially

treatment of rheumatoid arthritis where the number of different types of agents used is large, one must keep in mind the tendency for the disease to go into spontaneous remission, and any worker contemplating clinical evaluation of drugs in rheumatoid arthritis is advised to compare his results against the results of these authors, unless he is in a position to run an adequate control series. The difficulty, however, in running a true control series among patients with rheumatoid arthritis readily becomes obvious to the clinician, since such patients are constantly bombarded by advice on rheumatic disorders in the public press as well as from all manner of charlatans and others. It requires on the part of the patient the greatest perseverance and fortitude to maintain the status of "an untreated control"

In a somewhat unusual study, Nissen (56) presented the continuous follow-up study of 500 arthritics Among these 500, 100 had died. He divided those who died into four "courses" designated as *A*, *B*, *C*, and *D*. In course *A*, were patients who had had one attack of rheumatism, recovered from it, and returned to their former level of activity, at which level they continued without recurrence of joint disturbance until terminal illness. Course *B* represented patients who had remissions and relapses throughout life. They averaged 17.5 years of life after the onset. In the first group, the average was 27 years Course *C* were patients whose joint disease led to a definitely lower level of activity and continued at this lower level until death They lived an average of 19 years In course *D* were patients who showed a steady progressive joint involvement and increasing incapacity, practically without remissions until death. They lived an average of only seven years after the onset of disease and showed extensive systemic involvement. Nissen's study showed that in the entire group of arthritics, arteriosclerosis apparently developed at a younger age than in normals; moreover, this study was done before treatment with large doses of vitamin D was in vogue Among the 400 living, 65 developed clinical signs of arteriosclerosis, of which 25 showed heart abnormalities.

Mutch (57) made a comprehensive review of drugs in the treatment of rheumatic disorders He concluded that the most valuable measures in the treatment were (*a*) cleansing areas of surface infection, (*b*) correcting alimentary aberrations, (*c*) maintaining the efficiency of vital functions, (*d*) relieving pain and distress, and (*e*) chrysotherapy.

Simpson *et al* (58) evaluated the effect of multiple blood transfusions on rheumatoid arthritis Among their 60 cases in which plasma proteins were studied, fibrinogen values were high in 38, high normal in 16, and within normal in only 6 cases. Globulin values were high in 21 cases, 10 of these showing a concomitant low albumin figure All patients showed secondary microcytic anemia of varying severity and abnormal erythrocyte sedimentation rate Forty patients were given blood transfusions and 10 plasma infusion; three of the latter had whole blood transfusions in addition. Those given whole blood showed rapid improvement in hemoglobin,

and found that if the daily penicillin dosage exceeded five million units, the patient slowly improved. Coss *et al.* (73) investigated the prolonged administration of penicillin in rheumatoid arthritis and concluded that it was worthless. During treatment of 10 patients, seven developed brownish discoloration of the tongue, and bacteriologic studies demonstrated change of the predominant organism in the pharynx from gram positive to gram negative and disappearance from the throat of penicillin-sensitive organisms, as well as the appearance of coliform bacteria in the pharynx and decrease in the prevalence of gram positive diplococci in the intestinal tract. There was no apparent diminution in the incidence and severity of upper respiratory infections in this group. Rice *et al* (74) reported the ineffective use of streptomycin. Kuzell *et al* (75) reported the inffective use of aureomycin. Grino *et al.* (76) reported the favorable use of a combination of streptomycin and aureomycin in a case of dermatomyositis Brown *et al.* (77) reported clinical improvement in six of eight patients treated with aureomycin who had demonstrable urinary infection due to pleuropneumonia-like organisms (L-organisms) and in 13 of 17 patients without this infection. It is of considerable theoretical interest, however, that Barnard (78) described total daily dosage of 100 to 250 mg. of terramycin in single or divided doses was highly effective in intrinsic allergy, demyelinating neuropathy, malignant lymphoblastoses, and radiation myelopathy Smaller doses of terramycin, thus, may be worthy of trial in rheumatoid arthritis.

Hodas *et al.* (79) reported using glucuronic acid in rheumatic disease with favorable results Such results have not generally been confirmed by workers elsewhere. Perlman (80) reported the oral use of undecylenic acid in psoriasis and later in the arthritis associated with psoriasis. His report has not yet been confirmed by other investigators and the drug is poorly tolerated by many patients. LeGoff (81) reported on the sympatholytic action of cobalt and on the use of cobalt injections in patients with rheumatic disease. His results were favorable and deserve further investigation.

Novotny (82) reported the favorable effect of transplanting bits of diseased joint capsule under the skin of the lower abdomen in a patient with rheumatoid arthritis, following the idea of "desensitization" to the diseased tissue. He reported partial relapse several weeks postoperatively, but 9 of 11 patients so treated improved following the relapses Liebenson & Whittenborn (83) reported on the treatment of rheumatoid arthritis with the sodium salt of tetrathiodiglycollic acid (Anathion). The authors' contention was that sodium tetrathiodiglycollate releases sulfur at the tissue level when injected intravenously in aqueous solution and that the sulfur thus released reacts with the sulfhydryl compounds present in the tissue in the same manner as, in the authors' opinion, gold salts act, but without destroying these sulfhydryl compounds The reviewer has been unable to confirm this work in clinical trial. Blazer *et al.* (84) reported on the ineffectiveness of aluminum subacetate in rheumatoid arthritis, the fundamental idea being to reduce the level of blood phosphorus by combining with phosphates in the intestinal

eriod of observation. Three died of some other disease, nine changed to ironic polyarthritis, and seven were suffering from rheumatic valvulitis. Sinclair & Duthie (67) used salicylazosulfapyridine (Salazopyrin or Azopyrin) in 20 cases and concluded that the drug had no specific value in the treatment of rheumatoid arthritis. Kuzell & Gardner (68) reported on 30 patients with rheumatoid arthritis treated with salicylazosulfapyridine from two months to one year. Fourteen were symptomatically relieved in varying degrees. This group included seven patients not previously benefited by gold therapy and four who had had toxic reactions to gold. In spite of symptomatic clinical improvement, the ESR of each tended to remain elevated. Extension of the disease in patients under treatment appeared in only one patient. Continuation of small dosage for long intervals appeared to be important. Fourteen patients were not relieved symptomatically, but they became no worse. This group included eight with severe advanced disease, six of whom had not been benefited by gold therapy. One patient had a moderate reduction in erythrocyte count and hemoglobin The drug had little toxicity in rodents and was comparatively poorly absorbed in man. Bargen (69) noted the disappearance of the joint manifestations associated with ulcerative colitis while patients were under treatment with salicylazosulfapyridine.

Parr & Shipton (70) reported on the use of various sulfonamides in rheumatoid arthritis. They emphasized the use of small doses of various sulfonamides for long periods of time and particularly benzylsulfanilamide (Proseptasine) In their hands, low-dosage sulfonamide therapy for long-term use gave results at least equal to gold therapy Their work has not been duplicated extensively elsewhere, but it is certainly worthy of further investigation, since the earlier observations on sulfonamide therapy of rheumatoid arthritis emphasized the use of the so-called "full therapeutic" dosage, whereas these workers used doses of only 0.5 to 2 0 gm. per day and in some cases smaller dosage.

Ney (71) discussed the influence of roentgen irradiation on body defense mechanisms using, in nine cases of rheumatoid arthritis, wide-field "soft" x-ray irradiation The nine cases treated were all in an advanced state and had previously failed to respond to standard treatment Six showed low serum albumin and high serum globulin Following treatment, the six cases responded with clinical improvement and return of the albumin/globulin ratio to normal Two showed no clinical improvement, and the third improved belatedly In the six cases which responded, liver function tests were normal Definite abnormality was found in the two nonresponding cases and slight abnormality in the more slowly-responding individual. He indicated that "soft" wide-field x-ray irradiation could influence pathological albumin/globulin patterns in rheumatoid arthritis

The use of antibiotic substances has generally not met with much success in treatment of rheumatoid arthritis Klausgraber (72) demonstrated the presence of *Streptococcus viridans* in two patients with Felty's syndrome

coccus. The effects observed in 60 patients were similar to those observed in the treatment with vaccine. Small doses were well tolerated, but larger doses caused a so-called "focal reaction" with more pain, stiffness, swelling, headache, giddiness, and insomnia, lasting for a few days, when doses were too large. Phillips (97) reported on the clinical response to vaccine in 125 cases of rheumatic disease. The vaccine used was of three forms—*Streptococcus* (200 strains), *Staphylococcus* (2 strains), and the mixed stock vaccines containing both. He advocated low dosage and reported much improvement in 82 per cent of patients with myositis, fibrositis, and neuritis, 73 per cent of rheumatoid arthritis, 45 per cent of osteoarthritis, and 67 per cent in uric acid diathesis.

Fox (98) reported the somewhat strange situation that among 55 patients with rheumatoid arthritis, throat cultures revealed that 47 had no diphtheroid organisms present In throats of the healthy control patients, 46 per cent showed growth of diphtheroids, but among these controls were seven boys who had had symptoms of rheumatism, and six of these seven showed no diphtheroids. Clinical trials were made using a vaccine made of diphtheroids An analysis of results showed that, in a group including fibrositis, myositis, and rheumatoid arthritis (111 patients), 21 per cent were "cured," 55 per cent were "much improved," 17 per cent "improved" and only 7 per cent showed no change or were worse. Since vaccines are so widely used and so little studied, it seems urgent that some established organization, such as the American Rheumatism Association, might initiate carefully controlled studies on the value of vaccine in the treatment of rheumatoid arthritis An unusual report of the effectiveness of an "activated reduced sulfur" (#396) used intravenously in the treatment of rheumatoid arthritis was made by Reitg Puig & Rotés Queral (99) several years ago, but no other reports on its use have been found.

Warter (100) reported the use of hesperidin and ascorbic acid in 30 patients who each received 50 mg orally for six weeks, and he observed that the abnormal capillary fragility of patients with rheumatoid arthritis was normalized in 18. Nine showed improvement and became normal after three more weeks of treatment, and three showed no improvement Fluctuations in capillary fragility were observed following upper respiratory infection, stress, and after large doses of acetylsalicylic acid or amphetamine sulfate. Reversion to the original condition of capillary fragility occurred when the drugs were withdrawn The use of these compounds apparently did not alter the sedimentation rate or the blood count Wilson & DeEds (101) reported that hesperidin, a glucose derivative of hesperitin, prolonged epinephrine action considerably

Clark & Geissman (102) reported on the potentiation of effects of epinephrine by flavonoid compounds Rutin prolonged the recovery time of rabbit ileum treated with epinephrine, 3 1 times that of epinephrine alone They also made the interesting observation that gossyptin, 8-hydroxyquinoline, quercetin, 2′,3,4-trihydroxychalcone, glutathione, sodium tetraethyldithio-

tract and preventing their absorption. Repeated estimations of the blood calcium and phosphorus during treatment, however, showed no significant alteration.

Carlstrom & Lövgren (85) reported the use of adenosinetriphosphoric acid (ATP) in treatment of 144 patients with rheumatoid arthritis Of these, 66 per cent showed "marked improvement" or recovered completely. In 19.4 per cent, the recovery was such that it was not definitely attributable to ATP treatment, and 14.6 per cent showed no apparent response. The immediate effect of treatment with ATP was a decrease in serum citric acid and an increase in pyruvic acid. Values for serum iron rose to normal level after treatment with ATP, and the albumin globulin ratio was normalized in that the albumin increased and the globulin, particualrly the γ-globulin, decreased. They also pointed out that in hepatitis, there is often a rise in values for citric acid and serum iron, whereas in rheumatoid arthritis, these values are lower than normal. Further, in 93 necropsies of rheumatoid subjects, fatty changes in the liver were demonstrated in 42 per cent, amyloid degeneration in 8 per cent, and psoriasis in 11 per cent.

Heyman *et al.* (86) reported the transitory symptomatic relief of pain in rheumatoid arthritis using tetraethylammonium bromide. Howell (87) reported on the same subject and noted that in 26 patients, 16 were relieved temporarily. Rogoff *et al* (88) and Kling (89), Freyberg (90), and Solomon & Stecher (91) reported the use of antireticular cytotoxic serum in rheumatoid arthritis, spondylitis, and degenerative joint disease, and all concluded that this agent was of no benefit.

The use of nitrogen mustard in the treatment of rheumatoid arthritis was reported by Jiménez-Díaz (92) in treatment of 14 patients Eleven patients were given 4 mg every other day for six days, and three patients were given 5 mg every other day for 10 days. In the latter three, leukopenia and anemia developed. All 14 patients showed improvement in their rheumatic disease. The improvement was pronounced in nine patients who were in the group treated for six days

Ferrari & Allegri (93) reported the favorable use of Cafestol (a substance derived from the unsaponifiable fraction of the seed of *Coffea arabica L*). A small series of patients with rheumatoid arthritis improved under treatment, and in two patients with Hodgkin's disease, the lymph glands became progressively smaller

Organ extracts made from the liver and spleen of young sheep (AF-2) were investigated by Schwerdtfeger & von Uexküll (94) who described considerable but not complete relief of pain in four patients with advanced arthritis. Kersley & Simpson (95) reported the ineffective use of calcium *o*-iodooxybenzoate in a carefully controlled clinical evaluation of its effect in rheumatoid arthritis

In the prolix literature available on arthritis, there is evidently a current trend of investigators to avoid the investigation of vaccines. Barford (96) reported on the use of bacterial filtrates of mixed *Streptococcus* and *Staphylo-*

coccus. The effects observed in 60 patients were similar to those observed in the treatment with vaccine. Small doses were well tolerated, but larger doses caused a so-called "focal reaction" with more pain, stiffness, swelling, headache, giddiness, and insomnia, lasting for a few days, when doses were too large. Phillips (97) reported on the clinical response to vaccine in 125 cases of rheumatic disease The vaccine used was of three forms—*Streptococcus* (200 strains), *Staphylococcus* (2 strains), and the mixed stock vaccines containing both. He advocated low dosage and reported much improvement in 82 per cent of patients with myositis, fibrositis, and neuritis, 73 per cent of rheumatoid arthritis, 45 per cent of osteoarthritis, and 67 per cent in uric acid diathesis

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Clark & Geissman (102) reported on the potentiation of effects of epinephrine by flavonoid compounds Rutin prolonged the recovery time of rabbit ileum treated with epinephrine, 3 1 times that of epinephrine alone They also made the interesting observation that gossyptin, 8-hydroxyquinoline, quercetin, 2′,3,4-trihydroxychalcone, glutathione, sodium tetraethyldithio-

carbamate, and cysteine hydrochloride, were 16, 26, 10, 10.5, 9, 12 5, and 11 times, respectively, as high as *rutin in epinephrine potentiating activity.* They reported that concentration of 25 m. per 100 cc. rutin produced 50 per cent inhibition of the copper-catalyzed oxidation of epinephrine, and on a weight basis glutathione, sodium bisulfite, cysteine, British anti-Lewisite (2,3-dimercapto-1-propanol, BAL), and citrin were 1.4, 1.8, 3.1, 3.1, and 0 7 times, respectively, as active as rutin. Rutin plus ascorbic acid, on the other hand, had an activity of three to four times greater than that of either alone. The practical importance of these studies indicates that the empiric use of various substances such as ascorbic acid, rutin, sulfur-containing compounds, glutathione, and cysteine might actually alter the rheumatoid state in some manner by changing the response to epinephrine. This approach may deserve further investigation regarding the effects of these substances on the action of ACTH, cortisone, and related compounds.

Margolis & Caplan (103) evaluated the use of curare (*d*-tubocurarine in oil and wax) in the treatment of muscle-spasm of rheumatic disorders and concluded that it relieved muscle-spasm and indirectly the limitation of motion and pain in nonadhesive periarthritis of the shoulder, facilitated physiotherapeutic management, and shortened the period of treatment in adhesive periarthritis of the shoulder when manipulation under anesthesia was *necessary for breaking up adhesions.* Curare was found to be useful in the treatment of low back conditions associated with muscle-spasm but was of no benefit in patients with sciatic pain resulting from nerve root irritation or pressure. There was practically no effect in alleviation of muscle-spasm associated with advanced rheumatoid arthritis. Schlessinger (104) emphasized the importance of curare as an adjunct in rehabilitative physiotherapy, stressing that its use merely reduces the neuromuscular patterns He reported (105) on the use of myanesin (Tolserol), a brain stem and spinal cord depressant, as being of possible use in reducing spasticity, rigidity, and involuntary movement. He found that this was quite effective for a short time when the drug was given by vein but that gastric irritation prevented its effective oral use

Marton *et al.* (106) discussed the intravenous use of procaine as an analgesic and therapeutic procedure in painful chronic neuromusculoskeletal disorders and concluded that the analgesic effect was slight and transient. Among 33 patients, objective controlled evidence of lasting improvement followed repeated infusions of procaine in only one instance. Four patients showed moderate prolonged response or marked improvement only for the duration of the infusion. On the other hand, the reader is confronted with reports such as that of Cozen (107) where small doses of procaine solution (20 cc. of 0 5 per cent) were used intravenously in treating 108 patients and "temporary relief of pain and increased range of joint motion were observed in practically every patient," but he also administered, immediately prior to the drug, 1 oz. of whiskey by mouth.

Graubard & Peterson (108) reported a three year study of 250 patients

with a total of 894 procaine infusions using 4 mg. procaine hydrochloride per kilogram of body weight, the duration of the infusion being 20 min. Among these 250 patients were 54 rheumatoid arthritics, 42 arthritics due to trauma, and 154 osteoarthritics The results in respect to pain are classified as "good" in 199 cases, "fair" in 30, and "poor" in 21, while in respect to mobility there was "improvement" in 211 cases Graubard & Peterson supposed the mode of action was due to an analgesic action on the "dysfunctioning capillary unit" of the affected joint and the irritated nerve endings breaking the reflex arc pattern and permitting the return of normal circulation. Since they did not employ a graded system of evaluation of clinical results such as that of Steinbrocker and associates (54), the results described are impossible to interpret Dodd & Pfeffer (109) reported on the use of procaine in a similar fashion in 64 patients and noted that good results were not obtained in patients with rheumatoid arthritis but were appreciable in those with degenerative joint disease, traumatic arthritis, and myositis.

Cohen (110) advocated the use of carbon dioxide inhalation from an anesthesia machine until breathlessness, warmth, and dizziness occurred. After such treatment daily for a maximum of 48 days, the follow-up one to four years after treatment revealed 11 per cent unimproved, 6 per cent improved, but with the recurrence of symptoms, 6 per cent improved, and 77 per cent completely free of symptoms In view of this rather striking report of clinical improvement, there has been a singular lack of confirmatory evidence in the literature.

Epinephrine ointments have been advocated by Howell (111) in treatment of fibrositis "secondary to rheumatoid arthritis or osteoarthritis" These results were accomplished with the inunction of epinephrine in a strength of 1:5,000 in a base, the composition of which was not disclosed in the report The use of this ointment relieved pain for from 10 min. to five days, except in seven obese females in whom no benefit was obtained The usual duration of freedom from pain was 12 hr. They also used a 1 per cent ephedrine ointment (in a base of 20 parts emulsifying wax, 10 parts wool fat, 0.05 parts chlorocresol, and 100 parts water) on 78 subjects producing relief of pain lasting from 8 hr. to 8 days.

Thiosemicarbazone (Tb. I) was reported to be of value in the treatment of rheumatoid arthritis by Heilmeyer (112), who treated 52 patients with rheumatic and other inflammatory diseases all resistant to other known medication. Thiosemicarbazone failed in nine but lowered the sedimentation rate in 43 with a definite drop to almost normal in 17, a considerable decrease in 13, and a moderate decrease in 13. General improvement was excellent in 20, moderate in 12, and slight in 11 patients, usually paralleling the drop in ESR, but occasionally diverging as in carcinoma where ESR falls and the neoplasm is unaffected This drug, however, has a high degree of toxicity. Among 52 patients, 20 showed some toxic manifestations. The author observed that the parallelism in the effects of thiosemicarbazone and

ACTH might be due to a blocking of cortisone antagonists by the thiosemicarbazide formed on splitting of thiosemicarbazone by gastric juice.

An interesting group of reports has appeared regarding a preparation (Irgapyrin) which is a combination of diethylaminoantipyrine (Pyramidon) and 3,5-dioxo-1,2-diphenyl-4-*n*-butylpyrazolidin-sodium (Geigy 15903). The latter compound facilitates the solubility of dimethylaminoantipyrine and a preparation containing 15 per cent of each is used in the treatment of various diseases including rheumatoid arthritis. Wilhelmi (113) reported that the erythema of shaved guinea pig back produced by exposure to ultraviolet light was delayed by 2 hr. in treated animals and edema of the rabbit ear produced by the local application of croton oil was reduced Gsell & Muller (114) noted that in rheumatic disease, Irgapyrin promoted lessening of fever, vasodilation, reduction of pain, and a decrease in capillary permeability facilitating the resorption of fluid exudate from the tissues. The therapeutic response was so effective that they proposed that failure to respond to use of this medication may be used as a diagnostic test to exclude an active inflammatory rheumatic disease In 30 cases of acute rheumatoid arthritis, they claimed 27 good results Among 20 chronic rheumatoid arthritics were 14 good results and 4 medium results. All of four cases of ankylosing spondylitis responded well. The drug has also been favorably reported in treatment of iritis Two cases of Reiter's syndrome were favorably influenced with immediate fall in temperature, subsidence of local signs of the disease, and improvement in general condition. One case relapsed after, discontinuance of the drug but continuation of medication brought about "a complete and final cure" The authors even reported improvement in a patient with the Felty syndrome. Loewenhardt (115) reported favorable results in 27 cases, including subsiding of swelling, relief of joint pain, increased motility of the joints, and reduction of fever. In the treatment of seven cases of degenerative joint disease, only three showed any improvement. Stettbacher (116) reported on its properties of analgesia as an antiinflammatory agent and as an antipyretic. He noted that in cases of liver damage, the drug was poorly tolerated, and he regarded severe leukopenia and severe renal or hepatic damage as contraindications to its use No agranulocytosis or other pathological changes in the blood or urine were observed as a result of its use The ESR, moreover, tended to decrease. Belart (117) noted good immediate results in 9 of 14 cases of chronic rheumatoid arthritis, but these results were lasting in only one case He noted four good results in arthritis of the spine and three moderate results. Minor toxic reactions were noted in several instances.

Wilhelmi (118) noted that the toxicity of Irgapyrin was less than that of dimethylaminoantipyrine and that its analgesic effect surpassed that of other pyrazoles with exception of dimethylaminoantipyrine. In experimental fever produced by an injection of *B coli* in the rabbit, there was an antipyritic effect. Wilhelmi also demonstrated a pronounced histamine-detoxifying-effect on the peripheral vessels in the isolated intestine and the intact

animal. Kuzell & Schaffarzick (119) observed in 60 instances of rheumatic disorders a marked analgesic effect of Irgapyrin as well as a tendency for joint swellings to subside and for joint mobility to increase rapidly in rheumatoid arthritics. There was a striking relief of spasm and pain in ankylosing spondylitis and gout. They noted little change in the blood picture but observed the presence of drug rashes, salt and fluid retention, euphoria, nervousness, and many instances of localized cellulitis of the buttocks (and one case of a draining sterile abscess) following its intramuscular use. In general, they were able to confirm the optimistic reports of the Swiss and German investigators; but much further study needs to be done, and certainly the cases must be classified and evaluated over a long period of time according to the grading system of Steinbrocker (54) in regard to rapidity of action and extent of immediate relief. This drug is the only nonhormonal agent which compares favorably in many instances with ACTH and cortisone.

Recently, the value of intravenous iron in the treatment of hypochromic anemia associated with rheumatoid arthritis has been studied by Sinclair & Duthie (120) who reported on the use of Ferrivenin, a proprietary iron preparation for intravenous use. Among 23 cases of rheumatoid arthritis with iron deficiency anemia which did not respond to one month of treatment with iron by mouth, iron sucrose (Ferrivenin) elicited good response in 16 The authors felt that there was a greatly increased demand for iron by the cell systems of the body in cases of chronic infection, and for some reason the patients with rheumatoid arthritis are unable to obtain satisfactory utilization of iron administered orally In cases which responded well hematologically, the ESR was also observed to fall. A year later, these authors reported a follow-up of the first 23 cases and an additional treatment of 28 Of the 16 cases which improved in the first series, 15 maintained their improvement from 7 to 23 months with further administration of iron The three which relapsed responded favorably to a second course of intravenous iron. Twenty-two of 28 cases in the new series showed a good hematological response rising from an average hemoglobin of 70 to 84.3 per cent at the end of one month and to 87.1 per cent after three months Among 10 cases critically evaluated regarding fall in sedimentation rate, it was noted that in six cases showing a good hematological response, the ESR fell sharply. In five unaltered cases selected with hemoglobin values of 80 per cent or over but in whom the ESR was elevated, following 1 gm of intravenous iron, the ESR fell and the hemoglobin percentage rose. Further, they noted that concurrent use of intravenous ascorbic acid did not alter the trend of these results. They feel that the fact that a significant number of cases respond *to intravenous iron in* large doses suggests that the anemia of rheumatoid arthritis is due to an increase in the need of the tissues for iron which cannot be met by the oral administration of iron even though absorption from the gut is normal This, they feel, has something to do with the fact that in the presence of infection, iron given intravenously is rapidly removed from the blood If their interpretation of the results is correct, it

may possibly clarify the beneficial action of cortisone and ACTH through study of their effect on serum iron levels.

The use of copper salts intravenously and intramuscularly has been advocated largely by Forestier and his associates (121 to 124) who reported 35 favorable responses among 59 patients with rheumatoid arthritis after repeated series of intravenous injections with sodium-*m*-(allylcuprothiourea)-benzoate (Cupralène) or cupro-oxyquinolinediethylsulfonate (Dicuprène) They alleged that copper salts were more effective than gold salts in treatment of patients during the first year of the disease and that they were less toxic than gold and may be used for patients intolerant to gold salts Forestier also feels that these preparations are of use in the chronic arthritis associated with gout. Tyson *et al.* (125) evaluated sodium-*m*-(allylcuprothiourea)-benzoate in 20 patients with rheumatoid arthritis and concluded that there was no value of such therapy since the number of remissions corresponded to the customary per cent of remissions in untreated cases, and they noted further that painful cellulitis occurred when this preparation escaped from the vein O'Reilly (126) reported on the ineffectiveness of the use of copper salts in the treatment of rheumatoid arthritis. Kuzell *et al.* (127) noted, on using sodium-*m*-(allylcuprothiourea)-benzoate and cupro-oxyquinoline-diethylsulfonate in 31 patients with rheumatoid arthritis and evaluating the results according to the classification of Steinbrocker, that 7 per cent showed grade I therapeutic response and 13 per cent showed grade II therapeutic response, which is probably less than normal expectancy in untreated cases. In the arthritis associated with psoriasis, among nine cases treated, four showed no response and five fell in groups I and II, indicating the slight possible therapeutic value of these copper preparations in some such cases. The use of copper salts in two cases of Reiter's disease was followed by apparent cure. Kuzell *et al.* noted the development of transitory amenorrhea in two female patients under treatment; however, they observed that the copper preparations appeared to have little other toxicity.

As the years go by, the accumulated experience with gold therapy is much greater, and today gold is being used by many physicians without the great fear on the part of the patient and physician which existed some years ago. Gold is not a particularly safe medication unless given under close medical supervision, and its use does not bring about therapeutic benefit in every instance. It is the general consensus of opinion of most rheumatologists that gold is the best single agent in the treatment of rheumatoid arthritis at the present time, leaving to one side, of course, the new development of cortisone and ACTH which will be considered below.

Freyberg (128) evaluated the present status of gold therapy in rheumatoid arthritis and emphasized that the chief contraindication to the use of gold was previous severe gold toxicity. Gold salts should be used with great care in persons who are known to have idiosyncrasy to other drugs or who have allergic disease. Pregnancy is not a contraindication, although the arthritis is generally so much improved during pregnancy that gold

therapy is seldom concurrently considered. When another serious systemic illness exists, it is better cured or controlled before gold therapy is insti- [illegible]

He reported the therapeutic results of gold therapy in 18 series of cases which included 4,086 patients in which the range of improvement graded as "arrested or slightly improved" was from 40 to 84 per cent with an average of 61 per cent and "moderately improved" was 10 to 40 per cent with an average of 24 per cent, giving a total of moderately improved and greatly improved average of 85 per cent Sundelin (129) reported a series of 2,441 cases with improvement in 90 per cent. Freyberg (128) observed that various reporters estimated the incidence of gold toxicity anywhere from 4 to 51 per cent with an average of 37 per cent depending on the inclusion of the most minor types of reaction.

Hench (130) felt that a patient receiving gold had a 10 to 15 per cent chance of obtaining complete remission, about 50 per cent additional chance of being notably improved, and a 35 per cent chance of obtaining no significant relief. On the other hand, the patient has a 50 per cent chance of having no toxic reaction, a 45 per cent chance of having a minor or moderate reaction, and a 3 to 5 per cent chance of a serious but nonfatal toxic reaction, and about 1 chance in 250 of developing a fatal reaction (these statistics were assessed before the widespread use of BAL in gold toxicity). Tarnopolsky (131) reported beneficial effect of gold therapy in 85 to 95 per cent of cases treated. Parr (132) made the important reservation that the greatest success in use of gold salts was in the early cases and among those in whom periarticular involvement is present along with low ESR, and the least improvement or failure of therapy was noted in those patients in which the vasoconstrictive phenomena predominated. In a group of 200 cases treated by him and his associates, there was no relation noted between complications and the ESR Patients showing vasoconstrictive phenomena were the most likely to develop albuminuria and blood dyscrasias. Parr advanced the idea that beneficial action of gold was mediated through a combination of gold and sulfhydryl radicals, glutathione, or a gold cysteine complex compound

Adams & Cecil (133) reported a clinical study of patients with rheumatoid arthritis of less than one year's duration and not associated with psoriasis, ulcerative colitis, Felty's syndrome, or Reiter's syndrome; among these patients, there were disabilities in 99 per cent and elevated sedimentation rate in 90 per cent; the average age was 42 years, and the female to male ratio was 2:1. They received salicylates, rest and good hygiene, and were considered to be a control group. In addition, 106 patients were given one or more courses of gold with gold thioglucose (Solganol-B) or gold sodium thiomalate (Myochrysine). In the gold-treated group, 56, 90, and

100 per cent of the remissions began in 6, 12, and 24 months respectively, compared with 25, 44, and 80 per cent for the same respective period in the control group. The average period from the beginning of treatment to remission was 7.1 months in the gold group, and 17.1 months in the control group. Remissions were present in 66 per cent of the gold-treated patients and 24 per cent of the controls one year after beginning treatment. Their final results showed great improvement including remissions 77 and 61 per cent in the gold group and 59 and 39 per cent in the controls for the respective durations of the disease from 1 to 6 and 7 to 12 months prior to therapy. According to the therapeutic criteria of the American Rheumatism Association, there was complete remission in 45 per cent of the treated and 28 per cent of the controls, marked improvement in 13 and 10 per cent, slight improvement in 6 and 9 per cent, and unsatisfactory results (including 28 and 33 per cent relapses) in 36 and 54 per cent, respectively They noted toxic effects mainly as mild dermatitis and transient albuminuria. There was temporary alopecia in two and purpura simplex, leukopenia, exfoliative dematitis and enterocolitis, each in one patient Though they occurred in 49 per cent, they usually cleared rapidly when gold was withheld.

Kling (134) reported following 116 patients who had a remission or great improvement after the gold therapy. In five years, 57 per cent had relapses. Of 32 patients followed for 10 years, 75 per cent had relapses, but these relapses were only partial and amenable to further treatment. In estimating the duration of the relapses in these 116 patients, an average of one out of five years following treatment was spent in relapse, and among the 32 who were followed for 10 years, 3 years out of 10 were followed in relapse. Most rheumatologists, now being conscious of this relapse rate, do not give gold therapy in courses "but rather give it more or less continuously using small maintenance doses given every three or four weeks." Margolis et al (135) report on the use of an insoluble gold salt, aurothioglycolanilide, which was used in pellet form in treating six patients. Several of the pellets were extruded, and there was serum drainage from the wounds for several weeks. Intramuscular implantation was better tolerated. They implanted pellets whose total weight was 4 3, 6 0, and 4.3 gm, respectively, in three patients, and after seven months, there was striking subjective and objective improvement in these individuals. Friedman & Steinbrocker (136) reported on the intensive use of aurothioglycolanilide (Lauron) in rheumatoid arthritis with poor therapeutic results Robinson (137) reported that aurothioglycolanilide, aurothioglucose, and gold sodium thiomalate were of equal therapeutic use and that aurothioglycolanilide was of lesser toxicity than the other two. The reviewer was unable to treat successfully a case of gold toxicity due to aurothioglycolanilide with BAL, presumably because of the insolubility of the compound and its failure to combine with the antidote.

Nystrom (138) reported on a series of 762 patients treated with gold; he noted at the conclusion of treatment that 62 per cent showed improvement and 26 per cent were not improved. Complications occurred in 40

per cent, but in only 7 per cent was the complication severe enough to result in abandoning gold therapy Browning *et al.* (139) reported a more gloomy picture regarding chrysotherapy. Their series comprised 47 patients, and they noted that 23 per cent showed improvement, 62 per cent showed no appreciable change, and 15 per cent became worse. They noted that 62 per cent of patients showed toxic reactions, and among these were two cases of exfoliative dermatitis, with one death (before the advent of clinical use of BAL). Here again, when standard rating systems are not used, evaluation of clinical response is vague.

Parr & Shipton (140) reported basophilic stippling of the red corpuscles during gold therapy. Among 20 patients taken at random from a series undergoing gold therapy, basophilic stippling was shown in the erythrocytes of every patient irrespective of the age or sex or the variety of the arthritis. The counts varied from 200 to 6,500 stippled cells per million red cells. Generally speaking, there appeared to be a relationship between the extent of the basophilia and the severity of toxic reaction. Eosinophilia varying from 5 to 45 per cent was observed in 18 patients receiving intensive chrysotherapy by Reisner *et al.* (141): Steinberg (142) reported 50 manifestations of gold toxicity seen among patients receiving gold thioglucose. Bone marrow aspirations were done on these patients Eosinophilia appeared several weeks before gold rashes. Bone marrow eosinophilia was taken to indicate that unusual precautions should be instituted in further therapy. A fall in platelet count was an indication for doing bone marrow aspiration.

Fraser *et al* (143) advanced a rather disturbing report on the inaccuracy of colorimetric methods in determining the amount of gold in biological fluid They indicated that the variability of such methods of gold determination in duplicate and triplicate samples is of such magnitude that the results of all previous studies done by this method must be considered subject to question. The reviewer has noted as much as 50 per cent inaccuracy of the colorimetric method for determination of gold in urine and has found that the most accurate method for such determination is the use of fire assay techniques

Brecher & Waxler (144) reported the interesting observation that following a single injection of gold thioglucose, albino mice showed unusual weight gain, and careful study of the tissues showed that the weight gain was accounted for primarily by marked increase in adipose tissue At the end of 14 weeks, the average weight of males treated with gold was about 36 gm., whereas the controls weighed 26 gm The females treated weighed 30 gm and the untreated controls, 25 gm Kuzell & Dreisbach (145) showed that gold sodium thiosulfate was ineffective in combating histamine toxicity and did not prevent the development of the Arthus phenomenon in guinea pigs Bertrand (146) reported the predilection of radioactive gold for diseased joint tissue in experimental animals and in patients with rheumatoid arthritis as compared with normal joint tissue. Svanberg (147) reported a method for testing patients' sensitivity to gold prior to treatment which employed

intradermal injections of gold sodium thiosulfate in the skin of the back. In patients tested, an increased reaction was followed by complications in 19 out of 20 cases, and a decreased reaction was followed by no complications in 19 out of a further 20 cases. Of the remaining 16 which showed no change in reaction, *seven (44 per cent) had complications, and nine (57 per cent)* had none. Kempf (148) reported on the use of a new gold compound, gold-keratin-hydrolyzate (Auro-detoxin), with which he obtained 208 examples of marked benefit among 250 patients with rheumatoid arthritis Drug reactions occurred in only 7 per cent of his series. Halbertsona (149) reported on the gold treatment of chronic arthritis (Still's disease) in children. Six patients, aged 4 to 14 years, all responded favorably to the use of gold thioglucose. Five were completely cured, and one was left with some residual disability of the knee.

The use of BAL in the treatment of gold toxicity has now made possible the more widespread use of chrysotherapy. In the treatment of toxic reactions produced by soluble salts of gold, BAL is apparently quite effective as reported in many instances and in all varieties of toxic manifestations due to gold Davison (150) reported the use of BAL in dermatitis due to gold salts Lockie *et al.* (151) reported the treatment of thrombopenic purpura and granulocytopenia due to gold with the use of BAL. MacLeod (152) presented a critical review of the use of BAL in the treatment of gold toxicity. Experimentally, it has been shown that BAL promotes the urinary excretion of gold in rats and mice (153, 154, 155). Block *et al.* (156) studied *in vitro* the inhibition of oxygen consumption of rat kidney slices with gold sodium thiosulfate. They observed that this inhibition of oxygen consumption due to gold is not lessened by the potential thiol compounds, cysteine, methionine, nor by BAL or thiomalic acid which contains a thiol group. *However, the inhibition of oxygen consumption was lessened* by sodium thioglucose The effects of BAL and thiomalic acid were masked by the fact that these compounds in themselves produce inhibition of respiration. The *in vitro* inhibition of oxygen consumption in the rat kidney slices caused by gold chloride was appreciably reduced by thiomalic acid, BAL, *l*-cysteine, and sodium thioglucose, but not by methionine or cysteine

Kuzell *et al* (157) showed that the addition of methionine to the diet of rats receiving toxic doses of gold sodium thiosulfate was followed by an increase in the survival rate and that when methionine was added in the diet and BAL given intramuscularly, the survival rate was increased beyond that obtained using either substance along. *The animals receiving methionine* dietary supplement excreted less gold in the urine than those on the control diet. Histologically, the kidneys and livers of rats receiving *gold sodium* thiosulfate injections and treated with both BAL and methionine were much less damaged than the organs of rats treated with either alone. Dietary supplements of choline, cysteine, or washed sulfur gave slight, variable, or ineffective protection against gold poisoning, although choline and cysteine protected females somewhat better than males While methionine bene-

fited females more than males, gonadectomy, blank operations, and large doses of female hormones failed to demonstrate any correlation between sex and toxicity. Weil & Sichère (158) reported on the disappearance of intolerance to gold therapy following the implantation of estradiol or testosterone pellets. Kominz (159) reported the decrease in the incidence of toxic reactions due to gold when massive doses of ascorbic acid were given intravenously at the same time as the gold injections

Physiotherapy is the most neglected field in the treatment of rheumatic diseases in general. This difficulty is complex. It includes lack of sufficient training of the physician in methods of physiotherapy and its possibilities, a shortage of physiotherapists, and physiotherapy facilities. In the treatment of rheumatic diseases of all kinds, physiotherapy has a part in the treatment of almost every patient. Martin (160) recently outlined "what every physician should know about prescribing physical therapy." He evaluated the various methods available in physiotherapy such as heat, hydrotherapy massage, electric stimulation, therapeutic exercise, ultraviolet therapy, and he outlined the pitfalls in physiotherapy. Stengel (161) reported the use of sodium and magnesium sulfate solutions in iontophoresis for rheumatoid arthritis with beneficial results in over 90 per cent of patients. Kelly (162) outlined the possibilities of physiotherapy in treating the arthritic and indicated the importance of the adjunct use of ACTH and cortisone Currence (163) emphasized the practical application of local heat and concluded that hydrotherapy is pre-eminently the most desirable method for the use of local heat on the extremities. Jern & Currence (164) described the underwater use of ultraviolet light as a reliable sterilizing procedure in hydrotherapeutic practice Kendell *et al* (165) outlined the use of physical medicine in the home treatment of arthritis Clemmesen outlined the basic principles of remedial exercises (166).

Engel *et al.* (167) used a venous occlusion plethysmograph with the compensating spirometer recorder to study the effects of contrast baths on the peripheral circulation of 51 patients with rheumatoid arthritis. Contrast baths were given at water temperatures of 110° and 60°F. (43.3 and 15.6°C) beginning with an initial period of 10 min immersion in the hot water, alternating in the cold and hot every 1 and 4 min., respectively, and ending with the hot water, making altogether a total of 30 min. This procedure produced a maximal average increase in peripheral blood flow of 95 per cent in the upper extremities when these alone were treated, 62 per cent in the lower extremities when these alone were treated, and 170 per cent respectively in the four arms and legs when the four extremities were treated simultaneously. Forty-five minutes after the contrast bath to four extremities simultaneously, there was still an average increase in blood flow of 63 per cent in the forearms and 65 per cent in the legs There was an average increase of 0 3 to 0 5°C. in oral temperature as a result of these contrast baths to the extremities, the temperature increase being greatest in patients who received contrast baths to the four extremities simultane-

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fited females more than males, gonadectomy, blank operations, and large doses of female hormones failed to demonstrate any correlation between sex and toxicity. Weil & Sichère (158) reported on the disappearance of intolerance to gold therapy following the implantation of estradiol or testosterone pellets. Kominz (159) reported the decrease in the incidence of toxic reactions due to gold when massive doses of ascorbic acid were given intravenously at the same time as the gold injections.

Physiotherapy is the most neglected field in the treatment of rheumatic diseases in general. This difficulty is complex. It includes lack of sufficient training of the physician in methods of physiotherapy and its possibilities, a shortage of physiotherapists, and physiotherapy facilities. In the treatment of rheumatic diseases of all kinds, physiotherapy has a part in the treatment of almost every patient. Martin (160) recently outlined "what every physician should know about prescribing physical therapy." He evaluated the various methods available in physiotherapy such as heat, hydrotherapy massage, electric stimulation, therapeutic exercise, ultraviolet therapy, and he outlined the pitfalls in physiotherapy. Stengel (161) reported the use of sodium and magnesium sulfate solutions in iontophoresis for rheumatoid arthritis with beneficial results in over 90 per cent of patients. Kelly (162) outlined the possibilities of physiotherapy in treating the arthritic and indicated the importance of the adjunct use of ACTH and cortisone Currence (163) emphasized the practical application of local heat and concluded that hydrotherapy is pre-eminently the most desirable method for the use of local heat on the extremities Jern & Currence (164) described the underwater use of ultraviolet light as a reliable sterilizing procedure in hydrotherapeutic practice. Kendell *et al.* (165) outlined the use of physical medicine in the home treatment of arthritis Clemmesen outlined the basic principles of remedial exercises (166)

Engel *et al* (167) used a venous occlusion plethysmograph with the compensating spirometer recorder to study the effects of contrast baths on the peripheral circulation of 51 patients with rheumatoid arthritis. Contrast baths were given at water temperatures of 110° and 60°F. (43 3 and 15 6°C) beginning with an initial period of 10 min immersion in the hot water, alternating in the cold and hot every 1 and 4 min., respectively, and ending with the hot water, making altogether a total of 30 min This procedure produced a maximal average increase in peripheral blood flow of 95 per cent in the upper extremities when these alone were treated, 62 per cent in the lower extremities when these alone were treated, and 170 per cent respectively in the four arms and legs when the four extremities were treated simultaneously. Forty-five minutes after the contrast bath to four extremities simultaneously, there was still an average increase in blood flow of 63 per cent in the forearms and 65 per cent in the legs There was an average increase of 0 3 to 0.5°C in oral temperature as a result of these contrast baths to the extremities, the temperature increase being greatest in patients who received contrast baths to the four extremities simultane-

ously and least to those patients who received treatment to the legs only. Engel *et al.* (168) studied the effect of microwaves on bone and bone marrow and on adjacent tissues and demonstrated that it was possible to raise the temperature of submuscular bone marrow 3.0° and subcutaneous bone marrow 3 4°C. through use of microwave diathermy.

Nelson *et al* (169) concluded that ultrasonic radiation was capable of heating bone marrow and felt that this method presented possibilities as a form of diathermy. Wakim *et al.* (170) noted that active fever induced by intravenous administration of typhoid vaccine led to a reduction of peripheral blood flow during the chill phase, whereas physically induced fever, by the use of hot baths or the hypertherm, was consistently accompanied by an increase of blood flow and an increase of heart rate. Bach (171) presented a technique for the relief of pain in the arthritic hip. He injected procaine into the region of the obturator nerve on the affected side using a thin fine-bore needle 2 to 3 in. in length and 10 to 20 cc. of 1 per cent solution of procaine into the region of the nerve at a point immediately above the transverse process of the fifth lumbar vertebrae Injections were given every three or seven days for 6 to 10 times This method is used as an adjunct in physiotherapy. McDonnell (172) emphasized that faulty sleep posture is responsible for pain in the costo-vertebral articulations and outlined methods for their manipulation.

Fløystrup (173) conducted investigations upon the mechanism of indirect warming Heating the arms in a water-bath brought about a rise in the temperature of the toe pulp which depended upon an intact circulation to the toes When the circulation to the toes was blocked, the warming did not take place, thus indicating that this method depended upon a heat-transfer rather than a neurogenic phenomenon Edstrom *et al.* (174) described an interesting experiment in which the air of a hospital ward (Lund, Sweden) was constantly conditioned at 32°C and 35 per cent relative humidity Patients were treated in this atmosphere for 100 days, and the effect of the hot, dry microclimate was as follows the peripheral circulation increased in all, peripheral vasospasm was converted into peripheral vasodilatation, the relative oxygen saturation of venous blood measured at the medial cubital vein increased in the hot room, while the arterial-venous difference diminished At 20°C room temperature, they obtained a 51 per cent mean oxygen saturation, in the hot room, the result was 82 per cent mean oxygen saturation, the hemoglobin was unchanged, the cardiac output per minute showed no statistically significant changes in cases of normal heart function, but in cases with cardiac defect, the function of the heart was better, probably owing to diminished active peripheral resistance to blood flow at the higher temperature There was no change in the calorie consumption and basal metabolic rate in most cases. Cultures from the pharynx showed in most cases β-hemolytic streptococci on admission of patients to the hot room, but only in two cases were such cocci detected at the end of their stay Apparently, streptococci do not tolerate the hot dry

atmosphere of the microclimate The most obvious effects on the clinical symptoms have been remission of periarticular edema and capsular swelling

no tendency to immediate recurrence of symptoms after removal from the hot room.

Mennell (175, 176) discussed the place of manipulation in treatment of chest pain. There appears to be some merit in many of the manipulations. Demonstration of methods is probably of greater importance to the beginner than reading of them.

Hormones in Rheumatic Disease

Hench, Kendall, Slocumb & Polley (177, 178, 179) reported on the effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone, compound E, cortisone acetate) and of pituitary ACTH on rheumatiod arthritis and later on rheumatic fever and other related collagen diseases. They noted spectacular and rapid improvement in articular and muscular symptoms The sedimentation rates were reduced in some instances and upon withdrawal of these hormones, the disease manifestations promptly returned. Their first clinical trials of these substances began a new era in clinical medicine So spectacular were the effects of these substances in temporarily altering the manifestations of the collagen group of diseases that the Nobel Prize for Medicine in 1950 was awarded the physician Hench and to the chemists Kendall and Reichstein who had long before isolated compound E of the adrenal cortex.

Since 1949, several hundreds of studies have been completed on laboratory aspects of the use of these substances and related compounds in an effort to explain their mode of action in the collagen diseases and elsewhere Among the most heartening aspects of the use of these substances is the relief afforded to sufferers from asthma, various types of dermatitis, and iritis. Their importance lies in the ability to effect controlled remissions of several related diseases followed by "controlled relapses" on their withdrawal, permitting study of remission and relapse at will The mode of action of these substances is still mysterious, but much has been learned of possible alterations of normal and pathological physiology as well as of toxic manifestations during their use in men and many species of animals

The mere fact that the disease process again becomes manifest upon withdrawal of ACTH or cortisone is not *in itself a theoretic disadvantage if* one keeps in mind the use of insulin in diabetes mellitus Toxic side-effects of cortisone and ACTH are so considerable that some other agents must be found for effective treatment of large groups of patients with rheumatoid arthritis, gout, rheumatic fever, iritis, asthma, and the diffuse collagen diseases

Rosenberg (180) has evaluated the use of these drugs clinically and has

concluded that the degree of improvement appeared related to the intensity of the disease at the time medication was begun. The long-continued administration of both hormones proved practical and relatively safe in his hands when intermittent or discontinuous dosage schedules were employed. Even after long-continued medication, symptoms of rheumatoid arthritis generally became more active when either hormone was withdrawn. Subcutaneous rheumatoid nodules became smaller under the influence of either ACTH or cortisone, but these nodules did not disappear, and in every instance, enlargement recurred when the hormone was withdrawn. The effect on associated iritis resembled that on the articular symptoms and on nodules. Psoriatic arthritis, rheumatoid spondylitis (ankylosing spondylitis), and Still's Disease reacted similarly to ordinary rheumatoid arthritis. His group evaluated a number of other steroid compounds and found them to be ineffective for controlling the symptoms of rheumatoid arthritis. This group included testosterone, Δ^5-pregnenolone, 21-acetoxypregnenolone, 17-hydroxyprogesterone, progesterone, 17-hydroxy-11-desoxycorticosterone (Reichstein's Compound S), pregnene, triolone, and desoxycorticosterone acetate. They saw a water-retention tendency among those receiving ACTH and cortisone and used diuretics as necessary. Edema promptly disappeared upon cessation of medication. Acne occurred more frequently with the use of ACTH than with cortisone. ACTH produced acne in individuals of both sexes under the age of 40. Four of 10 patients treated with ACTH for more than 60 days developed deep pigmentation of the face and the exposed portion of the neck and hands. The color of this pigmentation resembled that of a sun-tan. Among Rosenberg's patients for the most part, there were no significant changes in blood pressure. They did not encounter the development of diabetes mellitus.

Carlisle *et al.* (181) pointed out that cortisone depresses ACTH secretion and causes adrenal-cortical atrophy (reversible when administration ceases) and is a depressant of adrenal-cortical secretion. On the other hand, adrenocorticotropic hormone depresses the secretion of ACTH by the pituitary and causes adrenal-cortical hypertrophy (reversible when ACTH is withdrawn). ACTH stimulates adrenal secretion of cortisone and other cortical hormones provided functional adrenal cortices are present. Carlisle and his group indicated, in summarizing the world-wide work of investigators, that a beneficial effect which often could be classed as dramatic was produced by cortisone in rheumatoid arthritis, rheumatic fever, rheumatoid spondylitis, Still's disease, acute lupus erythematosus, Addison's disease, asthma, uveitis, iridocyclitis, iritis, sympathetic ophthalmia, and psoriatic arthritis. He noted that encouraging effects, which require further evaluation, are produced in certain skin disorders, acute gouty arthritis, ulcerative colitis, dermatomyositis, angioneurotic edema, early periarteritis nodosa, penicillin hypersensitivity, and early scleroderma. At the same time, he indicated that cortisone in moderate dosage (100 mg. per day) has little or no effect on the

nitrogen balance. The urinary excretion of uric acid is enhanced, and in high dosage, serum potassium levels often decrease as a result of increased urinary excretion of potassium. Effects on sodium balance are variable, tending toward early sodium retention and followed by increased excretion later in treatment. Cortisone administration is followed by a drop in the urinary excretion of the 17-ketosteroids. Cortisone is known to decrease the tuberculin reaction in sensitized guinea pigs and has been observed to decrease antibody nitrogen (in rabbits) and to cause involution of lymphatic tissue in man and animals. Cortisone causes a temporary fall in the circulating eosinophiles.

In using cortisone for symptomatic relief of rheumatic diseases, it is important that adequate dosage be given. In the initial period, 100 to 300 mg. daily is required. Later smaller daily doses may be used or larger doses several times per week. Freyberg (182) conducted clinical trials with Compound S, progesterone, 17-hydroxyprogesterone, Δ^5-pregenolone, 21-acetoxypregnenolone, testosterone, and six other steroids. None has been found beneficial in their studies Boland & Headley (183) reported on the management of rheumatoid arthritis with smaller doses of cortisone. When the dosage was reduced to from 32 to 65 mg. per day, satisfactory improvement was sustained in 32 out of 36 cases Booster doses were necessary to maintain control of some of the patients in this group. In the entire group, 41 of 42 patients showed some evidence of side reactions while on doses of 100 mg., but only 3 of the 42 showed toxic symptoms when on the smaller maintenance doses. Edema was noted in 11, facial roundness in five, blurred vision in five, thyroid enlargement in three, and there were isolated instances of acne, hypertrichosis, hoarseness, amenorrhea, purpuric lesions, and pigmentation. Most patients experienced some form of psychic change usually proportional to the dose. Carbohydrate tolerance decreased in two patients, and two elderly patients had spontaneous fractures. The anti-rheumatic effects usually disappeared completely upon withdrawal of the cortisone Muscular weakness and exhaustion developed in four after cortisone was discontinued, but not in any who continued on maintenance doses

Kuzell & Schaffarzick (331) observed some degree of clinical improvement in all of 17 patients with rheumatoid arthritis under the influence of cortisone. Five patients with gout improved when treated during acute exacerbation, and two others worsened symptomatically. Sprague *et al.* (184) reported rapid clinical improvement in 33 patients with rheumatoid arthritis or rheumatic fever treated with doses of cortisone varying from 74 to 200 mg. per day. Copeman *et al.* (185) intensively studied five patients with rheumatoid arthritis under the influence of large doses of cortisone and reported that four of the five "dramatically" improved and one "markedly" improved They noted a fall in ESR and decrease of circulating eospinophiles in all patients They evaluated Δ^4-androstene-3,17-dione, Δ^5-androstene-3-ol-17-one, pregnenolone (3 hydroxy-Δ^5,20-pregnenone), and $\Delta^{5,16}$-pregnandien-

3-ol-20-one in rheumatoid arthritis and observed no significant clinical improvement in spite of increased urinary output of 17-ketosteroid in some instances.

Kendall reviewed the chemistry of cortisone (186). Thorn *et al* (187), in a critical review of clinical aspects of ACTH and cortisone administration, emphasized that diversity and apparent nonspecificity of the actions of adrenal steroids suggests some single fundamental action at the cellular level. Since the two most potent steroids, cortisone and its closely related natural precursor, compound F, are both surface-active agents, action on cell permeability may well prove to be the common denominator of their ubiquitous effect. Mirick (188) studied the production of antibody among the patients under treatment with cortisone and vaccinated with 1.0 cc. of a solution containing 0.06 mg. each of six pneumococcal-polysaccharides and noted no difference in the production of antibodies between these patients and untreated controls. However, the degree of induced skin sensitivity to *Pneumococcus* polysaccharide was depressed in some patients during treatment with ACTH or cortisone No consistent variation from the basal level of the γ-globulin fraction was seen in the sera of the control patients, but there was a consistent drop in the serum γ-globulin fraction of 13 of 14 patients whose values before ACTH or cortisone had been within normal limits, even though specific antibody against *Pneumococcus* was increasing at the time.

Beck *et al.* (189) noted that while administration of 75 to 100 mg ACTH per day caused a sharp increase in the urinary excretion of ascorbic acid in patients receiving from 75 to 100 mg. of that substance per day, no increase occurred during the administration of 100 to 300 mg. of cortisone Long & Favour (190) reported that 13 of 34 patients medicated with ACTH or cortisone failed to develop a tuberculin reaction to intradermal tests with purified protein derivative after 7 to 30 days of treatment; whereas, seven of these had developed erythema when tuberculin-tested prior to therapy Six had not been tested After the withdrawal of the hormones, 11 showed positive and two negative reactions Nelson *et al* (191) showed that cortisone protected 38 of 42 sensitized mice against challenging doses of antigen. Recant *et al.* (192) described an antipyretic effect of cortisone in rabbits given *Pneumococcus* vaccine and a *Pseudomonas* pyrogen. Simonsen (193) noted in guinea pigs a fall of complement from six to eight hr. after the injection of cortisone in 12 of 19 normal guinea pigs, while none of 22 controls showed significant changes of complement in the blood. In guinea pigs passively sensitized against horse serum, a dose of cortisone varying from 5 to 10 mg per kg administered six to eight hr before the shock dose caused a reduction of mortality but did not prevent the occurrence of symptoms of shock.

Teilum *et al* (194) reported a marked regression of the massive accumulation of plasma cells in the spleens of hyperimmunized rabbits and a decrease in the scattered accumulation of plasma cells in normal animals They saw

cytoplasmic changes in the reticulum cells of the perifollicular zone of the spleen with transition to a homogeneous prehyaline or hyaline substance with marked hyalinosis of the splenic reticulum proper in the perifollicular zone and around the vessels. They suggested that these changes indicated the influence of cortisone on the serologic defense reaction and showed that in disease of the mesenchymal tissue, cortisone caused a change from an active prehyaline phase characterized by accumulation of plasma cells and hyperglobulinemia to an inactive hyaline phase which they compared with the phasic development in sarcoidosis. Large accumulations of glycogen in the hepatic cells corresponded in morphological picture to the glycogen accumulation seen in von Gierke's disease. Blood studies in their animals showed a marked rise in α-globulin fraction and a less marked fall in the γ-globulin while under medication with cortisone Plotz *et al.* (195) noted the inhibition of the formation of granulation tissue in wounds of the rabbit ear and suggested that the beneficial action of cortisone and ACTH in mesenchymal diseases might be related to the depressive effect on host reactivity Spain *et al* (196) reported that cortisone retarded the macrophage response in mice They observed a reduction in the total cellular content of the spleen of mice treated with cortisone Stephens *et al* (197) described a striking increase in the urinary excretion of free histidine in patients medicated with ACTH or cortisone, a phenomenon which previously had been observed only in connection with clinical remission of rhemuatoid arthritis

The effect of ACTH in treatment of rheumatoid arthritis has been reported by many investigators Only a few of the reports can be considered in this review. Janus (198) noted that improvement in joint tenderness and grip reached a peak in 6 to 8 hr , drop in the circulating eosinophils in 4 to 6 hr , and that blood flow increased in the first 6 hr. then rapidly decreased at 8 to 12 hr following single injections of 25 mg ACTH With a single injection of 200 mg. of cortisone, joint tenderness and grip remained unchanged for 8 hr , and then the effect increased to a maximum at 24 to 48 hr. Decreases in circulating eosinophils and knee blood-flow were maximal at 24 to 48 hr Brodie *et al.* (199) reported that among patients with rheumatoid arthritis who were medicated with ACTH, there was a highly significant increase in urinary excretion of free threonine, lysine, and tyrosine, whereas, in cortisone-treated patients, there was excretion of significant amounts of threonine and tyrosine, but urinary lysine excretion was not significantly increased. On the other hand, arginine excretion was not significantly affected by either.

Hench *et al* (200) described the daily administration of 70 to 111 mg ACTH in divided doses for 11 to 87 days in six patients Marked improvement was observed in rheumatoid arthritics resembling that seen with cortisone treatment. The ESR tended to fall, although in a few cases, it increased again during treatment. Ragan *et al* (201) observed variable and increased urinary creatine excretion in eight rheumatoid arthritics during administration of ACTH An increased urinary excretion of uric acid was

observed in the same group. In those in whom the *Streptococcus* agglutination test was positive, the titer remained unchanged in all but one instance in which a positive agglutination changed to "doubtful." The sensitized sheep-cell agglutination test likewise only decreased in one of the eight patients. One patient among the eight had an elevated antistreptolysin-O titer which did not change during 27 days of treatment.

Pelner & Waldman (202) suggested the possibility that the action of ACTH and cortisone may be that of "occupying" or "engaging" one or more of the liver functions, thus combating "hyperhepatism" (whatever that may be). Duthie (203) suggested that under certain circumstances, the spleen secretes a substance which antagonizes the action of adrenal steroids; his conclusion was drawn from studies on a patient who had had the spleen removed because of thrombocytopenic purpura. He observed that capillary resistance rises very rapidly and falls more slowly to normal levels on treatment with ACTH Astrup *et al* (204) described the ACTH treatment of a 10-year-old girl with rheumatoid arthritis. At first a marked improvement was noted. Thereafter, when she was maintained on a daily dosage of 2 mg. for a month, the ESR rose to the initial value. She developed albuminuria and finally a severe nephrosis during which they noted a decrease in the serum proteins, particularly in the α-1-globulin. Later treatment of the same patient with 50 mg daily for three days brought about a long-lasting remission in joint symptoms, but treatment had to be discontinued because of the development of edema. Finally, the plasma protein pattern became that of nephrosis

Havermark & Nordenson (205) studied the hematological changes in a 62-year-old female rheumatoid arthritic treated with ACTH. They noted a slight increase in hemoglobin and erythrocyte count which promptly fell after treatment. Serum iron levels rose sharply during treatment but fell thereafter to their original level The white cell count rose from 6,000 to 12,000 and then fell. The mononuclear count remained unchanged. The eosinophil count was reduced from 125 to none during the first and from 272 to none during the second course of treatment. Marrow study showed an improvement in the hematopoietic picture and temporarily became almost normal. Effersøe (206) described a fall in protein values in certain salting-out intervals of the globulin in the course of ACTH treatment. This fall occurred more frequently when medication produced a good clinical result. Asboe-Hansen (207) reported a subsidence under the influence of ACTH of histochemically demonstrable hyaluronic acid of the connective tissue as well as reduction in the number of mast cells, which are interpreted as the "peripheral transmitters of hormonal action."

Green (208) observed that following the subcutaneous injection of 1 mg. of ACTH into mice, skin mitosis was depressed for several hours in a manner similar to that observed in post-ischemic shock He believed that the depression or suppression of mitosis in the formative cells from which the lymphocytes and other antibody-producing reticuloendothelial cells are

derived might depress or abolish the tissue antigen-antibody reaction and the resulting allergic inflammatory reaction.

Luft, Sjögren & Li (209) reported that the use of pure ACTH peptides produced a clinical response comparable to that of ACTH in a rheumatoid arthritic. Thirteen milligrams of ACTH peptides gave an effect comparable to that of 25 mg. ACTH protein. Wolfson *et al.* (210) reported the use of ACTH adsorbed on colloidal aluminum phosphate which permits the satisfactory treatment of patients with single daily doses rather than the usual multiple 4 to 6 hr. dosage schedule used with ordinary ACTH Kinsell (211) reported using a mixture of peptides prepared by partial peptic hydrolysis of whole ACTH followed by precipitation of all the remaining proteins. This substance proved to be active clinically in the same manner as ACTH.

Holbrook and his collaborators (212) described the extremely interesting observation that among 20 patients changed from regular maintenance doses of pig ACTH to beef ACTH at the same dosage, at least five developed resistance to pig but not to beef ACTH; however, one developed resistance to both pig and beef ACTH, which raised interesting speculations concerning the nature of these two different kinds of resistance factors. The same workers (213) evaluated administration of ACTH by various routes and reported ACTH was not absorbed well enough through the gastrointestinal mucosa to be effective. Using procaine ACTH (12.5 mg per cc.), they obtained the same measure of therapeutic efficacy as with divided doses of ordinary ACTH. Using long-acting ACTH (adactar-Armour—an ACTH adsorbed on colloidal aluminum phosphate), it was possible to maintain clinical improvement by giving some patients semi-weekly injections using double the average daily dose. Holbrook and associates also observed that beef ACTH did not dissolve in the adsorbent and, therefore, could not be administered by that method. Among their many patients, they noted no evidence of resistance to ACTH when the administration was intermittent, but when administration was continuous and prolonged, several patients manifested heightened resistance

Borden *et al.* (214) studied the histidine tolerance before and during administration of ACTH by using 500 mg histidine given intramuscularly as histidine monochloride Blood samples were tested at ½, 1, 2, and 4 hr following injection On the third day following tolerance test, ACTH was begun, and on the fourth day of treatment, the second histidine tolerance test was run In a patient with rheumatoid arthritis and in a normal individual, plasma levels of histidine, threonine, arginine, and lysine increased following the injection of histidine. The maximum increase in the plasma-level in both tolerance tests occurred during the first half-hour and returned to normal in 4 hr. In the patients with rheumatoid arthritis, the values for arginine showed a greater increase than those for histidine. In estimation of the amino acids in the urine, histidine as well as arginine, tyrosine, glutamic acid, and threonine all rose slightly in the first 6-hr collection. The 24-hr. urine showed no appreciable rise in histidine excretion. During the second

urine test after the administration of ACTH, excretion of histidine as well as threonine, tyrosine, and arginine tended to decrease in the first 6 hr. and showed no striking increase in the 24-hr. specimen. There was no apparent explanation regarding the increased plasma arginine values in the absence of an increased urinary excretion of that amino acid. Evidently ACTH does not lower the renal threshold for histidine.

Holbrook's group also studied the prolonged administration of ACTH (215). Among 30 patients maintained on ACTH continuously for 6 to 19 months, six patients were maintained in complete remission on doses of 10 to 40 mg. per day and without toxic manifestations. Twelve other patients maintained 50 to 75 per cent improvement with somewhat larger doses, but with occasional evidence of toxicity (edema and acne). Twelve other patients maintained less than 50 per cent improvement, even with larger doses, in spite of receiving in excess of 100 mg. per day. In this latter group, edema, acne, fatigue, and tachycardia have been constant problems Estrogen proved to be helpful in control of acne. Six of the group improved when receiving thyroid. All of the patients were kept on a low sodium diet and were given 3 gm. of potassium chloride supplement daily. These patients were thought to represent a group in which resistance developed to pig ACTH Three patients, originally selected for long-term study, who had positive Thorn tests (eosinophil response) were totally resistant to ACTH in doses up to 150 mg. per day. Markson (216) reported continuous treatment of two patients with ACTH for a period of five months without toxic effect; however, three days following the discontinuance of therapy, the patients reverted to their former clinical status

Toxic manifestations of cortisone and ACTH.—Ragan *et al* (217) described cortisone inhibition of granulation tissue production in the rabbit and suggested that the inhibition was due to impaired reactivity of the connective tissue. They suggested that this observation of delayed wound healing may serve as an assay method of compounds for possible empiric use in the treatment of mesenchymal or collagen diseases Creditor *et al* (218) also observed that during the hyperadrenalism induced by ACTH, there is an inhibition in wound healing. Blunt *et al.* (219) reported the delay in the gross-healing of experimental fractures of rabbits and the delay in the absorption of hematomata On the fourth day after fracture, there was histological evidence of retardation of all phases of healing in the cortisone-treated animals, and there was failure of connective tissue regeneration at this time, perhaps due to an inadequate blood supply or possibly directly due to the action of cortisone itself. Kuzell & Schaffarzick (331) reported the presence of one or more toxic effects in 21 of 32 patients receiving cortisone. These side-effects consisted mainly of hypertension, which subsided with reduction of the dose, in 10, sleeplessness and nervousness in six, and euphoria in seven Other effects were depression, psychosis, delayed fracture healing in three, transitory deafness, blurred vision, excessive salivation, and weakness. Gastrointestinal bleeding was noted in three and subcutaneous hemorrhage in two

of four patients. Beck *et al.* (220) noted the development of peritonitis during the ACTH administration, the drug evidently obscuring the diagnosis Steinberg (221) reported marked exacerbation of a previously healed peptic ulcer in a female patient medicated with ACTH. Baker & Whitaker (222) reported the delay in closure of skin wounds on direct application of hog adrenal extract dissolved in 25 per cent alcohol. Habif *et al.* (223) reported the presence of perforated duodenal ulcer associated with ACTH therapy. Behrman (224) reported four patients treated with ACTH and cortisone who developed skin manifestations of hyperpigmentation, acne, hirsuteness, rounded face, striae-atrophicae, delayed wound-healing, and flattening of keloidal scars

Laqueur (225) described the appearance of lumpy masses of basophilic hyaline material in the basophiles of the hypophysis (Crooke's granules) of patients who had received small amounts of ACTH and small to moderate amounts of cortisone prior to death These granules were identical with those seen in the human hypophysis in Cushing's disease and related conditions. Golden *et al.* (226) also reported Crooke's hyaline cytoplasmic granules in the basophiles of the human hypophysis as well as basophilic stippling of many of the chromophobe cells. They suggested the possibility that these changes reflected the storage of endogenous ACTH following stimulation of the adrenal cortex by the therapeutic administration of this hormone.

Robson *et al.* (227) reported an increase in capillary resistance following the use of ACTH. Molomut *et al.* (228) reported marked reduction in spleen size of mice receiving several small daily doses of cortisone. Histologically, there was reduction in size of Malpighian bodies and the number of cellular elements in the splenic pulp Antopol (229) using large doses of cortisone in mice, produced a striking lymphopenia, loss of body weight, atrophy of the thymus and spleen, diminution in the size of the adrenal cortex, salivary gland, hypophysis, and the hibernating fat-body. The anatomical findings corresponded to those of the alarm and adaptation phenomena of Selye, except for atrophy rather than hypertrophy of the adrenal cortex.

Smith *et al.* (230) reported that ACTH and cortisone prolonged the coagulation of blood in man and animals They showed the release of heparin or a heparin-like substance into the blood following the use of these drugs and suggested that this may be similar to the hyperheparinemia of anaphylactic shock They emphasized possible interrelationship of the mast cell with its heparin-production, the adrenal cortex, and the changes in the blood coagulability which may accompany the response to stress. Hoefer & Glaser (231) reported the development of abnormal electroencephalographic and neuropsychiatric changes in patients treated with ACTH Thirteen of 15 patients so treated showed electroencephalographic abnormalities. Nine of the [illegible]

bits on the fifth day of cortisone administration This lipemia gradually

paralleled the increase in blood sugar. Marked glycosuria occurred, and the islets of Langerhans developed lesions similar to those seen in diabetes mellitus. Holten & Lundbaek (233) reported the development of decreased sugar tolerance and glycosuria in two patients with ankylosing spondylitis who were receiving 60 to 100 mg. of ACTH daily. Similar changes were also reported by Conn *et al.* (234) in a study of the use of ACTH in three normal subjects.

During careful observation of the effects of cortisone on young male rats, Winter *et al.* (235) described cessation of growth, yet the cortisone medicated rats consumed 47 per cent more food than their controls. Regrowth of hair in a denuded area was completely suppressed. Six weeks of treatment produced a greater than 50 per cent adrenal atrophy involving the zonae fascicularis and reticularis, but the zona glomerulosa was practically unaltered. The cholesterol and ascorbic acid content of the adrenals was markedly reduced. The thymus became extremely atrophic, and the spleen was moderately reduced in size. Depot fat also decreased. Serum α-globulin was decreased and γ-globulin increased during treatment. Serum cholesterol and alkaline phosphatase were elevated, and within 10 to 17 days after discontinuance of the injections, the changes were all reversed.

Spain & Molomut (236) described more extensive lesions which were localized in experimental tuberculosis of guinea pigs medicated with cortisone as compared with unmedicated controls. Tuberculin reactions in the treated animals were more edematous than those in the untreated group, a finding which has been confirmed in mouse tuberculosis by Hart & Rees (237).

Oral administration of cortisone.—In most of the studies thus far, cortisone has been given by intramuscular injection of the saline suspension which contains 25 mg per cc. (Merck) Freyberg *et al* (238) and Kuzell & Schaffarzick (239) reported on the effectiveness of cortisone administered orally. There is no evidence of associated gastrointestinal irritation following the oral administration of cortisone Its clinical effectiveness is remarkable, varying from 1.25 to approximately 3 0 mg of the oral to 1 mg. of the cortisone by injection, as judged entirely by clinical response The use of cortisone tablets in divided doses throughout the day has made possible a more smooth regulation of the individual patient. The saline suspension of cortisone may also be taken orally although its taste is quite bitter Use of syrup of yerba santa masks the taste quite well.

Cortisone pellets —Thorn *et al.* (240) reported using asceptically prepared cylindrical pellets containing approximately 150 mg. of cortisone in 15 patients with Addison's disease Striking improvement was experienced following the implantation of the pellets. In these patients with Addison's disease, the pellets were used for three to six months, and their average daily rate of dissolution was approximately 0 5 mg. per 50 mg. implanted The possible use of such pellets in rheumatic diseases appears unlikely in view of the much larger dosage needed to effect relief of symptoms.

Cortisone and insulin.—Henderson *et al.* (241) treated 12 typical rheumatoid arthritics with combination doses of cortisone and 40 units of insulin daily for 10 days. Six of these experienced rapid clinical improvement. Symptomatic improvement was obtainable on higher dosage levels. No side actions to insulin were observed. In those receiving 50 mg. cortisone plus 20 to 60 insulin units per day, major improvement was noted or complete remission in 11 of 12 cases and minor improvement in one. This method deserves further investigation particularly in the treatment of ocular disease where elevation of blood sugar might possibly alter the course of chronic uveitis.

Shock therapy.—Kersley *et al.* (242) attempted treatment of active rheumatoid arthritis with hypoglycemic reaction five days weekly for three or four weeks. Marked clinical improvement was noted in 22, slight improvement in 9, no change in 9, and deterioration in one. Improvement characterized by a general feeling of well-being, improved mental outlook, lessening of malaise, increased appetite, diminished joint pain, and deep hyperalgesia, occurred after the first week of treatment and continued throughout the course. The ESR was not significantly altered during treatment. Fourteen patients showed an increase and three a decrease of 1 gm of hemoglobin per 100 cc. of blood. A significant fall of eosinophils occurred in 34 of the 36 adequately controlled patients 4½ hr. after maximum hypoglycemia, but there appeared to be no correlation between the fall in eosinophils and the degree of clinical improvement. Ten patients maintained marked and three moderate clinical improvement six weeks after treatment. Of eleven arthritic patients subjected to electric shock therapy combined with curare, three showed marked clinical improvement, two slight improvement, and five no significant change. Vogt (243) showed that the denervated rat adrenal showed the same fall in ascorbic acid after an injection of insulin as the normal controls, although under a more severe stress. She suggested that cortisone may act to inhibit the pituitary response to stress in patients receiving both cortisone and insulin.

Tagnon & Corvilain (244) demonstrated that the intravenous injection of insulin is followed by a decrease in the circulating eosinophiles of the blood in subjects with normal adrenals, but that this decrease is not obtained if glucose is administered with the insulin, showing that the stimulus in this instance is hypoglycemia and not the insulin itself. They failed to obtain a drop in eosinophiles in three subjects with Addison's disease and one with pituitary insufficiency, which showed that this response is mediated through the pituitary and the adrenal cortex. Brown *et al* (245) reported on the treatment of three severe diabetics who had rheumatoid arthritis coincidentally. They all responded well to use of ACTH or cortisone, which suggests that the effectiveness of the adrenal hormones in rheumatoid arthritis is not closely correlated with the gross manifestations of their metabolic functions and may be independent of these activities as we measure them at present.

Pregnancy blood and post-partum plasma.—Since the report of Barsi (246), concerning use of blood of pregnant women to transfuse refractory

cases of rheumatoid arthritis, there has been clinical interest in confirming his claims of marked therapeutic benefit. Considerable recent work by Granirer (247, 248) has emphasized the use of postpartum plasma rather than whole blood in the treatment of rheumatoid arthritis. He reported 320 postpartum transfusions without any cases of homologous serum hepatitis The longest remission following therapy was 16 weeks and the shortest, three weeks. He noted that postpartum plasma had a greenish tint, was slightly opalescent, and homogeneously distributed. A study of the pooled plasma showed an average protein value of 4 35 gm. with an albumin/globulin ratio of 0.9. The lack of correlation between plasma protein levels and edema in the pregnant woman was striking. The proteins of the postpartum plasma resemble those of the *maternal sera at or near term.* No clear explanation of the ameliorating effect of postpartum plasma in the treatment of rheumatoid arthritis is apparent He also reported treating a man with rheumatoid arthritis with psoriasis in which both conditions improved simultaneously. Granirer has reported no ill effects of the use of postpartum plasma and has followed 24 patients for a period of two years giving 200 cc. infusions as needed.

Other steroids in rheumatic disease.—Lewin & Wassen (249) reported the combined use of intramuscular injections of desoxycorticosterone acetate *and immediately following the injection of 1 gm. ascorbic acid* intravenously. He noted increased warmth, marked alleviation and disappearance of pain of joints, and improved mobility, which persisted ½ to 6 hr. in 12 patients, 12 to 24 hr. in four, and 14 to 18 days in two. Several others have reported moderately favorable results with this technique. Hallberg (250) in addition to the desoxycorticosterone injected 8 cc. of 5 per cent methylene blue intravenously. He also reported similar results to the use of intramuscular desoxycorticosterone acetate and intravenous ascorbic acid. He observed no improvement when desoxycorticosterone acetate was used alone and *suggested that the results were due to an oxidation product of* that substance. Landsberg *et al.* (251), using the same treatment, felt that only patients in whom the arthritis was associated with loss of weight, depressions, vasomotor disturbances, and loss of locomotive power were likely to benefit from the method of Lewin. Because of the somewhat favorable early reports, there was a widespread use of this combined treatment throughout the country Due to the lack of effect of this method of treatment in the hands of most rheumatologists and others, a flood of articles of a condemnatory nature have appeared These include the articles of James *et al.* (252), Bywaters (253), Wessman (254), Kling (255), and Copeman (256).

Thyroidectomy and arthritis—Bach (257) discussed a case in which, following thyroidectomy for thyrotoxicosis, there was an onset of severe rheumatoid arthritis within one month. He proposed that with the partial thyroidectomy, there was a sudden cutting down in production of ACTH producing the picture of rheumatoid arthritis

Antistiffness factor.—Lansbury *et al* (258) studied the effect of the

"anti-stiffness factor," a fat-soluble vitamin concerned with regulation of phosphorus and calcium metabolism Animals deprived of this substance develop a syndrome characterized by muscle degeneration and stiffness, calcinosis (both interstitial and circumscribed), and the general characteristics of collagen diseases (fever without infection, increased ESR, eosinophilia, and reverse of the albumin/globulin ratio), as well as histologic lesions of collagen necrosis. The antistiffness factor prevents development of these changes, or if present in early stages, will reverse them. The use of this substance in scleroderma has been followed by only the most feeble beneficial effect and none at all on calcinosis The sources of this substance are green vegetables, raw cream, unheated molasses, and raw sugar cane juice Ross and associates (259) have shown the presence of this substance in sugar cane juice

Pregnenolone and other steroids.—In 1948 and 1949, Davison *et al.* (260) began to use in rheumatoid arthritis 3-hydroxy-Δ^5,20-pregnenone which is now simply referred to as pregnenolone They advocated the daily usage of 50 to 300 mg. intramuscularly in rheumatoid arthritis and ankylosing spondylitis and reported reduction of the urinary 17-ketosteroid excretion after a few days in the patients with ankylosing spondylitis. They claimed that the change in 17-ketosteroid excretion was accompanied by increased mobility in the spine when fixation was primarily due to spasm, but among those patients with low urinary 17-ketosteroid excretion, the response was slower. In five with "moderate" to "very-acute rheumatoid arthritis" involving only the joints of the extremities and four with "mild" to "severe" ankylosing spondylitis, initial improvement was noted after 3 to 16 days and complete absence of symptoms and objective signs after 3 to 36 days. It is difficult to assess the report critically since the American Rheumatism Association "therapeutic criteria" were not applied to the cases studied. Of the 30 patients discussed, only 13 were reported in detail Pregnenolone has been widely used by others, and although little evidence of clinical toxicity has been manifest, the number of investigators reporting improvement of rheumatoid arthritis with its use is singularly small in contrast to the large number of workers who report the complete lack of effect of this substance in rheumatic disease

Freeman and collaborators (261) reported on a series of 30 rheumatoid arthritics and noted that 15 of these had considerable diminution of pain, decrease in swelling, and increase in mobility and functional capacity in less than a week on oral doses of pregnenolone of 300 to 700 mg. per day. These changes were not always paralleled by changes in the ESR or in the level of circulating eosinophiles On discontinuation of medication in eight, six were given placebos Of these, three had recurrence of symptoms in four days to five weeks, and the remaining five maintained their improvement from two weeks to four months Of the remaining 15 patients, 11 were reported to have mild improvement, and four, in whom the disease had progressed extensively, showed no improvement. Later, Freeman *et al.*,

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Antistiffness factor.—Lansbury *et al.* (258) studied the effect of the

in six classical cases of rheumatoid arthritis. Polley & Mason (270) reported the ineffectiveness of 12 steroids other than cortisone and four adrenal-cortex extracts which were tested in 11 rheumatoid arthritics both with and without associated spondylitis. It is interesting that 10 of the patients had received cortisone and/or ACTH prior to the test and had had excellent antirheumatic relief, whereas they had no relief with the substances tested, including desoxycorticosterone acetate and pregnenolone.

Kling (271) reported a series of 40 patients with rheumatoid arthritis of the peripheral joints treated with progesterone or pregnenolone for one to four weeks and noted remission in five and major, minor, or no improvement in 11, 9, and 15 respectively. He also noted toxic effects consisting of disturbances in the menstrual cycle of 11 of 19 women, postmenopausal uterine bleeding in 2 of 12 women, and mild skin reactions in five. Alexander & Duthie (272) observed the administration of large doses of progesterone to five patients with rheumatoid arthritis without evidence of therapeutic benefit. Kyle & Crain (273) reported on 14 patients with active rheumatoid arthritis treated with progesterone or anhydro-hydroxyprogesterone for periods of 12 to 40 days with clinical remission occurring in one patient on two occasions with each drug, but they also noted in two patients a comparable remission following the use of an inert placebo.

Kersley *et al.* (274) made a clinical evaluation of various steroids including ethinyl estradiol, methyltestosterone, testosterone propionate, and progesterone and desoxycorticosterone in rheumatoid arthritis both used alone and in conjunction with ascorbic acid. In no instance was there any decrease of circulating eosinophiles or increase in the urinary uric acid-creatinine ratio to suggest any corticoid effect. They also noted that there was no relation between the saturation with ascorbic acid and the therapeutic results. The route of administration of ascorbic acid showed no correlation with the saturation of the therapeutic effects Only 4 of 42 cases showed any pronounced improvement maintained for more than 48 hr. Kersley & Mandel (275) in a further study supplemental to the previous one, administered progesterone with riboflavin as well as ascorbic acid and concluded that it was doubtful whether riboflavin or ascorbic acid showed any superiority over the use of saline solution. Riboflavin was tried instead of ascorbic acid in the second study because of its widespread use in the body tissues

Ishmael and associates (276) treated 90 patients with rheumatoid arthritis with mixtures of testosterone propionate, estradiol esters, and pregnenolone and noted improvement in 81 of the 90 patients However, they also did not avail themselves of the simple classification of cases and the therapeutic criteria advocated by the American Rheumatism Association, rendering the picture somewhat difficult for others to understand There are no other confirmatory reports in the current literature of the striking clinical improvement which these authors reported. The same authors, in a subsequent report, altered their conclusions to the extent that they claimed 45

reporting on a group of more than 40 patients with rheumatoid arthritis where the daily oral dose of pregnenolone was 500 mg. per day, noted striking improvement in 50 per cent after a period of one to two weeks, mild improvement in 30 per cent, and no improvement in 20 per cent. They reported an increase in urinary output of 17-ketosteroids. Cohen *et al* (262) reported that in over 300 rheumatoid arthritics treated with pregnenolone, 75 per cent showed subjective and objective improvement. Robles Gil (263) claimed improvement in 22 of 30 patients treated with pregnenolone.

Guest (264) reported treating 19 patients with pregnenolone from 7 to 51 days; with one exception, there was no consistent subjective or objective improvement. In April, 1950, the *Journal of the American Medical Association* (265) commented editorially that pregnenolone, epinephrine, combinations of testosterone, estrogen, and pregnenolone, and desoxycorticosterone acetate with ascorbic acid have not produced symptomatic remission in rheumatoid arthritis comparable to that obtained with cortisone and ACTH. Stock & McClure (266) reported significant and measurable improvement in only one of seven patients with typical established rheumatoid arthritis given 17-acetoxy-Δ^5,20-pregnenone. Stone (267) reported the complete absence of effect of pregnenolone in a group of patients who had all improved previously with ACTH. Fitch *et al.* (268) used 21-acetate of 3,21-dihydroxy-Δ^5,20-pregnenone (Artisone) in 15 patients and noted "very marked improvement" in nine, moderate improvement in three, and no improvement in three. Other investigators have not been able to repeat this work with the same degree of clinical improvement being noted. Generally speaking, there may be a slight degree of improvement in general well-being of patients given large doses of pregnenolone derivatives, but there is no clearcut evidence that these substances have any specific effect in the treatment of rheumatic disease. More carefully controlled investigative work should be done using untreated controls where possible instead of using each patient as his own control. It is indeed regrettable that the premature use of these substances became so widespread before they were even well into the investigative phase. As Bywaters has written (253): "The path of therapeutic advance is strewn with the bones and the bottles of those who have neglected such precautions."

Various other steroid substances have been used empirically in treatment of rheumatoid arthritis during the past two years in a frantic and seemingly hysterical attempt on the part of many investigators to find some hormone substance which would favorably alter the progress of rheumatoid arthritis—a disease first recorded by the ancient Egyptians No outstanding results have been obtained except where sex hormones have been used at the time of the climacteric in both male and female in order to improve the general physical well-being irrespective of the rheumatic disease present Terry & London (269) reported on the use of pregnenetriolone diacetate, 17-α-hydroxyprogesterone, and Compound S of Reichstein and noted no effect on any of the observed clinical, chemical, or hematological manifestations

"status thymico-lymphaticus." However, the small percentage of failure of the epinephrine test in this group of 51 patients would seem to indicate presence of a normally reacting hypothalamic-pituitary-adrenal-cortex system in the great majority of cases of rheumatoid arthritis, and they point out that the universal benefit of cortisone in rheumatoid arthritis on one hand being considered against the small percentage of cases showing lymphocytosis in the same disease, militates against the assumption of the concept that there is imbalance between the suprarenal cortex and the thymicolymphatic system in every case of rheumatoid arthritis.

Parr & White (280) described the treatment of rheumatoid arthritis with injections of epinephrine, using 0 5 mg. in oil twice daily. They claimed the apparent beneficial action might have had something to do with the production of adrenal cortical hormones, the resultant decrease in lymphocytes with the production of euglobulin which might, in turn, have some relation to immunological changes in these patients. Godlowski (281) also reported the favorable use of epinephrine and repeated insulin hypoglycemia in the treatment of rheumatoid arthritis. He felt that the epinephrine probably asserted its beneficial action through the stimulation of the adrenal gland to produce cortisone which in return exerted a beneficial action which should be regarded "as a non-specific but very potent factor in regulating the essential mechanism of the inflammation itself, but not affecting the etiology of the disease."

Thorn *et al.* (282) noted that the status of the adrenal cortical function appeared to be essentially normal in 16 of 21 patients with rheumatoid arthritis and that there appeared to be a wide variation in the state of adrenal cortical function from patient to patient with no apparent correlation to the degree and severity of the rheumatic disease present. They also felt that the improvement in gout which was brought about by ACTH was apparently not directly related to the renal excretion of uric acid but, in some direct way, to the diseased joint tissue Wallis & Horvath (283) have observed that the rise in systolic pressure following intravenous injection of 0 01 mg of epinephrine was impaired in the presence of excessive numbers of circulating antibodies and "therefore, presumably, excessive numbers of tissue-fixed antibodies"; this effect appeared to be independent of the serologic specificity of the antibodies The authors hypothesized that the physical presence of these antibodies in large numbers impeded the rapid contraction of arteriolar constrictor muscle Among the subjects with this impaired blood pressure response to epinephrine were patients with active, severe, typical rheumatoid arthritis. Wallis has also shown that patients with rheumatoid arthritis present electrophoretic evidence of excessive numbers of circulating antibodies

17-Ketosteroids excretion—The measurement of the urinary 17-ketosteroid excretion has been accomplished in several groups of patients with rheumatoid arthritis, gout, and ankylosing spondylitis. Davison *et al* (284) reported

per cent of patients improved when treated with testosterone and only 20.5 per cent of patients improved when treated with pregnenolone. Interestingly enough in their second (and as yet unpublished) report, they noticed dizziness, sore breasts, vasomotor instability, and skin eruptions as possible toxic side effects among patients treated with pregnenolone

Abnormalities in Adrenal and Steroid Metabolism

One approach to the problem of rheumatic disease has been the more or less indiscriminant use of every available hormone in massive dosage in attempts to alter the course of rheumatoid arthritis, rheumatic fever, and related collagen diseases An examination of the evidence for abnormalities in steroid metabolism associated with rheumatoid arthritis, however, reveals much less available literary production. Sommerville (277) studied the urinary excretion of pregnanediol in rheumatoid arthritics following the intramuscular injection of progesterone. The percentage of the administered progesterone recovered as urinary pregnanediol in normal men varied between 9 and 15 per cent in four cases, whereas in four male rheumatoid arthritics, it varied between 22 and 27 per cent. In normal post-menopausal women, in six instances the percentage varied between 12 and 16; whereas, in post-menopausal women with rheumatoid arthritis the percentage varied between 19 and 36. The authors stressed the importance of using their extremely sensitive method for the determination of pregnanediol in the urine. The discovery of this abnormality in the metabolism of progesterone among rheumatic subjects is of the greatest interest. The study deserves to be expanded to larger groups of patients with all types of rheumatic disease The authors indicate that even though this abnormality may prove to be specific for rheumatoid arthritis and related diseases, it may prove to be quite unrelated to the response of these conditions to cortisone therapy. Parr (278) emphasized the pronounced effect of cortisone and ACTH on the thymus and emphasized the absence of rheumatoid arthritis in Addison's disease.

Parr and his associates (279) have described the results of the epinephrine test in 51 cases of rheumatoid arthritis. They injected epinephrine hydrochloride in 0 5 cc of 1·1,000 concentration subcutaneously and eosinophile counts, total leukocyte counts, and differential leukocyte counts were made at the end of 1, 2, 3, and 4 hr They emphasized that the typical response to epinephrine in a normal person can be characterized by an increase in total leukocytes, total neutrophiles, a decrease in total lymphocytes, and 50 per cent or more decrease in total eosinophiles during the 4 hr of the test. Fourteen per cent of 51 cases showed an absence of the typical eosinopenia regarded as an expression of inadequate cortisone secretion in response to epinephrine. A pre-epinephrine lymphocytosis existed in 26 per cent of the patients, and the presence of enlarged lymph gland in both Still's disease and frequently in adult rheumatoid arthritis as well as the lymphocytosis is suggested as indicating a possible mild degree of the so-called

hard to describe whether the psychic disturbance or the rheumatism is the patient's disease. Even more suggestive in patients who already have rheumatoid arthritis, the appearance of a new stressor tends to cause a remission Selye re-emphasized the observations of Hench that occasionally rheumatoid arthritis is beneficially influenced by a variety of typical systemic stressors such as surgical operations, starvation, febrile reactions to foreign protein, pregnancy, or icterus. Although Bassi & Bassi (291) reported favorable influence of an adrenal cortical extract in rheumatoid arthritis in 1946, it was not until in 1948 and 1949 that Hench was able to show the striking suppression of the symptoms of rheumatic disease with the application of the cortisone and ACTH available to him at the time.

The future lines of research toward explaining the mode of action of cortisone and ACTH in the collagen diseases will probably proceed simultaneously in several directions. The review of the current literature, however, indicates that two lines of approach show particular promise. In the first place, the evaluation of the effect of ACTH and cortisone on serum iron levels should be correlated with the clinical findings of Sinclair & Duthie (120b) that intravenous iron used in rheumatoid arthritics is followed by a decrease in the sedimentation rate, a rise in hemoglobin, and a disappearance of the rheumatic symptoms. If more iron is required by diseased or sensitized tissue and is, thereby, not made available to the erythrocytes, it is likely that the beneficial action of gold and possibly some other substances may in "substitution" satisfy the need of diseased tissue for excess iron, leaving that substance available for the erythrocytes. Similarly, it may be possible that cortisone and ACTH block in some manner the chemical stimulus for iron to migrate to diseased tissue. Apparently, there are no studies available on the levels of free sulfhydryl groups and glutathione levels in rheumatic subjects before, during, or after treatment with various agents and while the rheumatic subject is under the influence of stressor agents Further, it is remarkable that there has been no critical evaluation of the status of the thymus in relation to the collagen diseases in spite of the flood of publications on related subjects and in spite of the fact that it is now well recognized that pregnancy, nitrogen mustards, various steroids including cortisone, and x-ray will bring about changes in the status of the thymus gland It is a well-known observation of physicians and sufferers from gout that the eating of thymus (sweetbreads) is often times followed by an exacerbation of gout. Another possible approach to the problem is nutritional, since there has been no correlation of the sulfhydryl content of the various food substances in regard to their ability to exacerbate gout and rheumatoid arthritis, although again it is a time-honored clinical observation that asparagus, which contains mercaptides, will occasionally exacerbate a chronic or latent gout

In regard to investigation of possible agents of infection with respect to rheumatic disease, it is possible that the further investigation of the role of the L-forms of pleuropneumonia-like organism in man would be re-

increased excretion of urinary 17-ketosteroids in male and female patients with ankylosing spondylitis whereas those with rheumatoid arthritis of the peripheral joints tended to have urinary 17-ketosteroid excretion of average magnitude.

Tarnopolsky *et al.* (285) noted that among nine women between the ages of 33 and 63 years, the figures for 17-ketosteroid excretion varied between 5.7 and 16.4 mg. per 24 hr. using the Dussich modification of the Talbot method. Sprechler (286) noted that when values for 17-ketosteroid excretion were plotted against the logarithm of the dose of ACTH, a linear relationship was found. He also observed in most of his cases a greater percentage increase in urinary corticoid excretion than in 17-ketosteroid excretion among those under treatment with ACTH. This difference was particularly marked in infants as compared with adults

Desmarais (287) reported the estimation of neutral urinary 17-ketosteroids using the Callow-Zimmermann method in 36 female and 31 male patients suffering from rheumatoid arthritis Among these, 75 per cent and 77 per cent, respectively, fell within the normal limits of excretion He found a significant correlation between urinary 17-ketosteroid excretion and the age of the patients in both males and females. There was in the male a significant correlation between the activity index and the 17-ketosteroid excretion, but this was not demonstrable in the female, and the reason for the discrepancy is not immediately apparent Davison and his collaborators indicated that during deep x-ray therapy (284b), there was evidently a stimulus for increased incretion of 17-ketosteroids followed by a relative decrease, and those patients whose disease was in the active phase apparently tended to show higher levels of urinary 17-ketosteroid excretion than in the more or less inactive or arrested cases.

Edstrom (288) reported on the treatment of rheumatoid arthritis with implantation of the anterior portion of calf pituitary glands in 26 cases which were relatively new and of moderate severity. In those patients under 40 years of age, the results were good, but in those in the older group, the results were less favorable. In six cases which became symptom-free, the effect was apparent almost immediately and was accompanied by a marked excretion of urinary 17-ketosteroids and a decrease in the eosinophiles of the circulating blood Fellinger (289), reporting on the implantation of fresh pig pituitary tissue on 62 occasions in 23 cases of rheumatoid arthritis, claimed some degree of clinical relief in 19 but stated that the relief was rapidly manifested and of only short duration. The laboratory findings showed leukocytosis with diminution in eosinophiles and leukocytes, reduction in ESR, and increased urinary excretion of urate and 17-ketosteroids

Selye (290) suggested that rheumatoid arthritis might be a manifestation of the General-Adaptation-Syndrome in response to a variety of nonspecific stressors among which are allergic reactions, focal infections, and psychosomatic derangements. He pointed out that in many cases, the onset of the disease is obviously correlated with emotional disturbance giving rise to the frequently used term "psychogenic rheumatism" in which case it is

more sensitive than the usually performed procedure using whole blood. Six milligrams of uric acid per 100 cc. of serum is taken as the upper limit of normal, whereas, 4.0 to 4.5 mg. per 100 cc. is taken as the upper normal limit of blood uric acid determinations. Tophi occurred in not more than 50 per cent of cases in his series and then only relatively late in the course of the disease. Aspiration of nodules was a rewarding diagnostic procedure where aspirated material revealed the uric acid crystals.

Talbott (296) emphasized that rheumatoid arthritis and gout may be observed in the same patient, and in such instances, each disease should be treated independently. Although gout is usually associated with a normal complement of red cells and hemoglobin, Morlock & Rosenberg (297) reported a case of coexistence of tophaceous gout and nontropical sprue Berk (298) reported an unusual case of gout in a young man who began to have typical severe attacks at the age of 11, and when seen at age 28 for a period of 17 months, never had a blood uric acid level over 4 0 mg. His diet had never been high in purine content. The roentgenograms displayed extensive bone and joint destruction. Kersley (299) reported the case of a man who died at the age of 23 from malignant tophaceous gout causing subluxation of the first and second cervical vertebrae due to tophaceous softening. In this patient, the plasma uric acid rose to 17 mg per 100 cc. without renal impairment, and the blood cholesterol fell to 50 mg per 100 cc. Post-mortem examination showed tophaceous softening of the cervical vertebrae and massive deposits of urates in nearly all the joints and many of the muscles

Harkavy (300) emphasized the allergic factors in gout. In his study of three patients, two men and one woman, he demonstrated that apparent allergic response to specific foods and pollens as well as infections played a conspicuous role in the development of acute gouty manifestations associated with elevations of blood uric acid He was able to produce typical attacks of gout by the subcutaneous injection of several pollen extracts or by the synergistic action of allergenic foods and pollen In one patient, he reported temporary urinary suppression and albuminuria following the exacerbation of joint symptoms subsequent to the injection of pollen. In another, an overdose of pollen produced nasal and pulmonary manifestations as well as acute gouty arthritis. He felt that the gouty individual of the type he described should be considered an allergic patient whose joints constitute the major shock tissue and who have a coincidental uric acid diathesis

The heredity of gout is important in the study of the pathological physiology of uric acid It has long been recognized that among the families of gouty patients, there is a high incidence of elevated blood uric acid in individuals who have no arthritic symptoms. Stecher *et al.* (301) reported an interesting study of 248 serum uric acid determinations on the 201 members of 44 gouty families, as well as, 1,024 serum uric acid levels on 961 patients examined routinely at the Cleveland City Hospital They took the upper limit of normal for serum uric acid to be 6 5 mg. per 100 cc and found

warding since here again it is known that the addition *in vitro* of glutathione or BAL to media will promote the growth of these organisms. Further, it is known that in the use of BAL to combat gold toxicity in rheumatoid arthritis, the symptoms of the rheumatic disease are oftentimes exacerbated, presumably by the free sulfhydryl groups of the BAL. There is almost nothing known about the immunology of pleuropneumonia-like organism in man which is not surprising since the media routinely used for the culture of pathogenic microorganisms in the hospital laboratory are not adequate for a growth of these organisms which are so small that they have to be studied in colony form. It appears, therefore, that cortisone and ACTH, which make pleuropneumonia infection worse in experimental animals and also cause experimental tuberculosis to spread more rapidly, may possibly do this through bringing about changes in the available sulfhydryl groups *in vivo* for the satisfaction of the growth requirement of the offending pathogen Here again, the striking efficacy of gold salts in the prevention or cure of pleuropneumonia arthritis in rats, in contrast to the failure of most other substances, may in some strange way be linked to the availability of the sulfhydryl group or to the presence or absence of glutathione in the oxidized or reduced form When one keeps in mind the foregoing observations, it becomes apparent that the action of cortisone may be simply to block the pathological requirement of some enzyme system which has been altered due to an infectional agent or other stressor.

GOUT

Gout is not a rare disease. It is commonly unsuspected or misdiagnosed. Talbott & Lockie (292) emphasize that gout has been considered to be rare because of failure to recognize its existence prior to the advanced stages and that atypical cases, particularly those with several joints involved, are often incorrectly diagnosed as some other form of polyarticular arthritis. Nissen (293) reported 251 instances of elevated blood uric acid among 1,500 patients with various types of arthritis In this group of patients with elevated blood uric acid, only 8 per cent showed x-ray changes typical of gout. All of the patients had a favorable response to the administration of colchicine, sodium salicylate, and glycine (gelatin). Among these 251 patients, not one gave a family history of gout, four had previously recognized gout, only three had tophi, and not one passed a urate stone

Rosenberg & Arens (294) emphasized that in the x-ray diagnosis of gout, the evidence of change is not to be expected until fairly late and that among every group of gout patients, there were many who showed no x-ray evidence of urate deposits in the joints. Kelly (295) emphasized that in gout, hyperuricemia is not a constant finding, in fact, it is often transient or absent in the early stages of the disease Usually, although not always, it is present in the chronic phases of the disease. The degree of elevation of blood uric acid, moreover, does not necessarily parallel the severity of the arthritic symptoms Kelly emphasized that serum urate determinations are

more sensitive than the usually performed procedure using whole blood Six milligrams of uric acid per 100 cc. of serum is taken as the upper limit of normal, whereas, 4 0 to 4.5 mg. per 100 cc. is taken as the upper normal limit of blood uric acid determinations. Tophi occurred in not more than 50 per cent of cases in his series and then only relatively late in the course of the disease. Aspiration of nodules was a rewarding diagnostic procedure where aspirated material revealed the uric acid crystals.

Talbott (296) emphasized that rheumatoid arthritis and gout may be observed in the same patient, and in such instances, each disease should be treated independently. Although gout is usually associated with a normal complement of red cells and hemoglobin, Morlock & Rosenberg (297) reported a case of coexistence of tophaceous gout and nontropical sprue. Berk (298) reported an unusual case of gout in a young man who began to have typical severe attacks at the age of 11, and when seen at age 28 for a period of 17 months, never had a blood uric acid level over 4 0 mg. His diet had never been high in purine content. The roentgenograms displayed extensive bone and joint destruction. Kersley (299) reported the case of a man who died at the age of 23 from malignant tophaceous gout causing subluxation of the first and second cervical vertebrae due to tophaceous softening. In this patient, the plasma uric acid rose to 17 mg. per 100 cc. without renal impairment, and the blood cholesterol fell to 50 mg. per 100 cc Post-mortem examination showed tophaceous softening of the cervical vertebrae and massive deposits of urates in nearly all the joints and many of the muscles

Harkavy (300) emphasized the allergic factors in gout. In his study of three patients, two men and one woman, he demonstrated that apparent allergic response to specific foods and pollens as well as infections played a conspicuous role in the development of acute gouty manifestations associated with elevations of blood uric acid. He was able to produce typical attacks of gout by the subcutaneous injection of several pollen extracts or by the synergistic action of allergenic foods and pollen In one patient, he reported temporary urinary suppression and albuminuria following the exacerbation of joint symptoms subsequent to the injection of pollen. In another, an overdose of pollen produced nasal and pulmonary manifestations as well as acute gouty arthritis He felt that the gouty individual of the type he described should be considered an allergic patient whose joints constitute the major shock tissue and who have a coincidental uric acid diathesis.

The heredity of gout is important in the study of the pathological physiology of uric acid. It has long been recognized that among the families of gouty patients, there is a high incidence of elevated blood uric acid in individuals who have no arthritic symptoms. Stecher *et al* (301) reported an interesting study of 248 serum uric acid determinations on the 201 members of 44 gouty families, as well as, 1,024 serum uric acid levels on 961 patients examined routinely at the Cleveland City Hospital They took the upper limit of normal for serum uric acid to be 6 5 mg. per 100 cc and found

elevated serum uric acid in the relatives of gouty patients as follows: 18 per cent among 11 mothers, 17 per cent among 24 brothers, 21 per cent among 24 sisters, and 15 per cent among 33 sons. Not a single daughter among 45 tested was found to have hyperuricemia. Among male relatives in the study, there was no correlation between age and hyperuricemia, but female relatives were not affected below the age of 50 which suggests the inhibitory effect of normal menstruation.

The genetic peculiarities of hyperuricemia are such that in some families it resembles an autosomal recessive, whereas, in others it is more like an autosomal dominant. These peculiarities are, however, quite satisfactorily explained if the gene involved is an autosomal dominant which lacks penetrance in both sexes, but has a much lower penetrance in the female than in the male. A tentative estimate of the penetrance is about 84 per cent in the heterozygous male, about 12 per cent or less in the female. This conclusion brings the data of the pedigrees in good agreement with a tentative estimate of the gene frequencies in the general population

Stecher further indicated that elevation of blood uric acid in itself is not enough to guarantee an attack of gout, and that patients with uremia, leukemia, polycythemia, pneumonia, malignancy, cardiac failure, and hemorrhage often develop elevation of blood uric acid even higher than that usually seen in gout without developing joint symptoms or tophi. Thus, there is apparently an unidentified factor or perhaps factors in the explanation of the pathological physiology of gout which remains unexplained and which may be unrelated directly to the blood level of uric acid.

Smyth *et al.* ... icemia in
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zygotes for this factor developed recognized gouty arthritis. Sex and age were also significant factors affecting the level of serum urate, and these factors must be taken into account in classifying relatives into "normal" and "hyperuricemic" groups. Males who possessed the abnormal hereditary factor apparently seldom developed marked hyperuricemia before the age of puberty When males under 16 years of age were disregarded, the proportions of hyperuricemic male relatives approached those expected on the assumption that heterozygotes are invariably hyperuricemic. By reducing the critical level for hyperuricemia from 6 mg. in males to 5 mg. per 100 cc. in females, the proportions of hyperuricemic females still fell somewhat short of the expected value.

Ishmael (303) reported on the familial aspects of gout, diabetes mellitus, and obesity His study showed that 43 per cent of the 56 patients with gouty arthritis investigated were from diabetic families Seventy-one per cent of this group listed obesity as a family characteristic Since there is such a difference in the clinical picture of diabetes and gout, he pointed out that faulty fat metabolism with the production of ketosis may precipitate the usual complications of either disease. The younger the patient at the

onset of the disease, the more severe the subsequent clinical course. Nephritis is often a final complication. Furunculosis appears frequently as a complication and may lead to the diagnosis of either gout or diabetes mellitus. Furthermore, the same factors are likely to produce exacerbations, i e. infections, surgical procedures, exhaustion, ketosis, emotional upsets, and exposure.

Spitz *et al.* (304) reported a fulminating fatal gout in a 47 year-old male who had not had joint symptoms prior to three years before hospital entry. His blood showed 1.7 million erythrocytes and a hemoglobin of 4 5 gm. per 100 cc. The spleen was quite enlarged and the liver slightly enlarged. Postmortem examination showed sclerosis and calcification of the portal vein and its main tributaries, as well as the usual manifestations of gout. The etiology and pathogenesis of the portal vein sclerosis and calcification remained obscure in this case, but this most unusual occurrence served to emphasize that gout must occasionally be suspected even when the blood count is low. He also advanced the consideration that the disappearance of the so-called old fashioned gout of 100 years ago was due to the discontinuance of the medical practice of bleeding. Anemia may provoke attacks of gouty arthritis but it is not among the common etiologic factors, since few people suffering from chronic anemia develop clinical gout

Brown & Mallory (305) recently have described the renal changes in gout by presenting the necropsy findings in five proved cases and one unproved case. All kidneys showed significant or marked benign nephrosclerosis and deposits of urate in the medulla, probably originally in the collecting tubule. One of their cases showed typical kidney changes but no clinical or joint manifestations of this disease, and the authors suggested that this case might represent "primary renal gout." Two of their cases showed marked pyelonephritis and one of these patients died in uremia. Another case showed small focal areas of healed pyelonephritis, and a fourth case was suggestive of the same. They suggested that tubular blockage by urates predisposed to pyelonephritis which might contribute to the renal damage commonly observed in gout.

Tarnopolsky *et al.* (306) reported the determination of urinary 17-ketosteroids in gout They found normal excretion in seven of eight patients, and in one, the excretion was 34 mg in 24 hr (using the analytical method of Talbot). Wolfson *et al.* (307) reported 10 cases of gout in men where the 17-ketosteroid excretion was measured, and among those, seven who had interval gout excreted 3.1 mg per 24 hr. Three patients with acute gouty arthritis had 3.5 mg. per 24 hr , and one woman with interval gout had 0 7 mg. per 24 hr. This was in contrast to their average of 12.0 mg. for males and 9.0 mg for females in normal individuals and 10.0 and 4 7, respectively, for rheumatoid arthritics. These authors concluded that, in view of the fact that their male patients with one exception showed normal biologic androgen activity, the finding of low urinary 17-ketosteroids constituted a finding characteristic for gout They assumed further that in gout, biologic androgen

activity might be maintained by an unusual androgenic hormone which does not make an important contribution of *urinary 17-ketosteroids* when it is metabolized.

These same authors (308) expressed the thought that this unusual androgen is important in the conversion of latent genetic hyperuricemia into actual elevation of plasma urate and in the male is not present before puberty and in the female until after the menopause. The differences in the excretory rate of urate (higher in the male) may therefore be explained by presence of a normal androgen. The presence of latent genetic hyperuricemia is, of course, essential in their theory of activity of the hypothetical androgen which presumably is of adrenal origin. They commented on the observation that virilism does not occur in gouty women and that there is no evidence to suggest hyperandrogenism in gouty men. In acute exacerbations of gout, they feel that there is a temporary relative 11-oxysteroid lack. Much remains to be clarified, although this is an attractive line of approach to the problem

The same authors, in discussing the clinical findings among 18 women with gout, conclude that there is a marked difference between tophaceous and pretophaceous gout in the female. In the first place, tophaceous gout in women begins before the menopause and is associated with more impairment of renal function and higher levels of blood uric acid. A family history of gout was obtainable in half of those with tophaceous gout, whereas it was obtainable in only one-fourth of those with pretophaceous gout, which suggests that the earlier onset and greater severity of the tophaceous type was due to genetic factors. The characteristic body habitus of gout in the female appears to be that of marked obesity and relatively short stature.

Wolfson and his associates (309) further concluded that the application of a battery of sensitive liver-function tests to a group of patients with gout gave no indication that there was any associated functional hepatic impairment among them During the acute attack of gout, the protein findings are occasionally altered in the γ-globulin fraction. The serum globulins are produced by the entire reticuloendothelial system, and the alteration in their levels cannot, therefore, be taken to mean alteration of liver function in individuals with active gout, since in other diseases altering the serum globulins, this finding is accompanied by alteration in other manifestations of liver function They also reported that there was a fall in serum cholesterol during acute gouty arthritis and that the serum cholesterol of gout patients tends to be highest just before the onset of gouty arthritis. These high levels may persist for some time after the onset. They feel that this is a manifestation of temporary adrenocortical hypofunction.

Selye (310) summarized the work of various authors in indicating that a variety of stressors such as physical trauma, infection, chilling, foreign protein therapy, x-irradiation, and so forth have been known to be precipitating causes of acute gouty arthritis. These agents are effective in producing an alarm reaction with the corresponding ACTH discharge Thus, it has been suspected that the acute gouty attack may be related to

this systemic response to stress. ACTH given during an attack of gouty arthritis causes the joint manifestations to subside promptly. On the other hand, if ACTH is injected during the interval period, patients predisposed to gout will show an acute exacerbation several days after the injection. Since colchicine can control an acute gouty episode, there has been considerable speculation about the relationship between the action of *Colchicum* and ACTH in gout. The administration of colchicine immediately after the discontinuation of ACTH impedes the rebound of acute arthritic manifestations which follow the withdrawal of ACTH.

The studies of Margolis (311), Benedict (312), and Bishop *et al.* (313) suggest that colchicine and ACTH act through distinct mechanisms in gout. These studies, in part, are based upon the use of N^{15} uric acid. If the theory of Wolfson and his associates is correct, and in gouty individuals the administration of ACTH results in the production of an abnormal testoid, this substance remains to be identified. The use of ACTH in single doses of 50 mg. is capable of bringing about a rapid improvement in acute gout followed by increased excretion of urates and rapid subsidence of clinical manifestations of the disease Generally within 36 hr., however, a decided rebound of gouty symptoms may develop.

The use of ACTH in gout apparently does nothing to alter the ultimate course of the disease. Bishop *et al.* (313) showed that in one patient with a uric acid pool size of 3,300 mg. (3 times normal), colchicine caused a 50 per cent decrease in pool size and an increase in turnover rate of from 0.50 to 1.01 pools per day. In a similar patient, cortisone decreased pool size 30 per cent and increased turnover rate from 0.59 to 1.26 pools per day. Another patient with a similar pool size showed no response to these two drugs; he had been maintained on a small daily dose of colchicine for some time These studies were accomplished using uric acid labeled in the 1- and 3-positions with N^{15}, this substance being injected intravenously into gouty patients during gouty attacks before and after therapy with colchicine and cortisone.

Talbott (292) made the clinical observation that an acute attack of gout may be preceded by a period of diuresis during which abnormal amounts of water, sodium, potassium, and calcium chloride and phosphate are removed from the body. The cause of such cyclic changes in the electrolyte turnover is unknown Hellman (314) reported that the use of ACTH in four patients was followed by an increase of urinary uric acid and nitrogen excretion and a decrease in sodium and chloride excretion Three patients had glycosuria, and two had increased glomerular filtration, renal plasma flow, and uric acid clearance. For three days following the injection period, there was an increased excretion of sodium and chloride while the uric acid returned to its initial value. Attacks of acute gouty arthritis developed three or four days after the completion of injection. The relief of symptoms, however, following injection usually appeared in 48 hr , whereas formerly, in the same individuals, attacks had lasted 10 to 14 days.

Wolfson *et al.* (315) reported on the use of ACTH in treatment of 38

gouty patients. They also used colchicine in a dosage of 0.65 mg. four times daily coincidentally with ACTH and continued its use after ACTH was discontinued. Relief in their cases sometimes occurred rapidly starting in 2 to 3 hr. after the first, second, or third dose and sometimes more gradually with increasing improvement following each successive dose. Attacks were usually ended within 24 hr. An average of 98 mg. of ACTH was required for 75 to 90 per cent relief of symptoms in the entire group. One hundred and twenty milligrams were needed in 21 attacks in chronically colchicinized patients or those previously treated with colchicine unsuccessfully compared with 70 mg. in 17 attacks not treated with colchicine before ACTH was given. A single 100 mg. dose of ACTH as the long-acting aluminum phosphate adsorbed ACTH with colchicine given simultaneously according to the above schedule ended five attacks in patients not previously given colchicine and in seven of eight colchicine-resistant attacks The remaining attack was ended by a second dose of ACTH given 24 hr. after the first. Improvement was noted in an average of 9 hr. in patients previously not receiving colchicine and an average of 13 hr. in colchicine-resistant attacks. They suggested that in certain medical and surgical emergencies, the prophylactic use of ACTH or cortisone is indicated to support the impaired mechanisms for mobilizing resistance to stress which is characteristic of gouty individuals Kuzell & Schaffarzick (331) reported the use of cortisone acetate in the treatment of seven patients with gout, five of whom improved when treated during acute exacerbation and two of whom became much worse.

In treatment of gouty arthritis, Forestier (316) reported on 21 subjects treated with gold salts, using a dosage of 100 mg. per week for 6 to 12 intramuscular injections. Usually two or three series of injections sufficed to improve these patients clinically. Thirteen of the 21 patients showed rapid improvement, and eight others were improved only after from four to five series of gold injections Eight other cases of more recent origin were given copper therapy, either intravenously [sodium-*m*-(allylcuprothiourea)-benzoate; Cupralène] or intramuscularly (cupro-oxyquinolinediethylsulfonate; Dicuprène) and in doses less than those usually employed in polyarthritis. The clinical impression in these preliminary observations was favorable Kuzell *et al* (127) treated 18 chronic gouty arthritics with the same copper salts and noted marked improvement in nine, slight improvement in five, and no improvement in five. Exacerbations of joint symptoms occurred less frequently after copper therapy

The injection of uric acid in rabbits in which the blood sulfhydryl content was reduced by about one-half following a feeding of methionine and cysteine deficient produced diabetes in 10. The other two were not affected, even by a third injection The uric acid diabetes lasted 5 to 10 days and was then cytologically similar to mild alloxan diabetes (317). Bien & Troll (318) reported that in the quantitative determination of urinary uric acid, the presence of glucose interfered.

Marshall and his group (319) investigated the antidiuretic effect of cin-

choninic acid derivates. The most active compounds tested were the 2-phenyl and 2-methyl derivatives of 3-hydroxy-4,8-quinoline dicarboxylic acid. They also showed that the concentration of ascorbic acid in the adrenals of the Sprague-Dawley rats 2 hr. after the subcutaneous administration of 200, 100, and 50 mg per kg. of 3-hydroxy-cinchophen sodium salt was 221 ± 12.4, 340 ± 36 6, and 355 ± 28 3 mg per 100 gm of adrenal, respectively, and with 50, 25, and 12 mg per kg of disodium-3-hydroxy-2-phenyl-4,8-dicarboxylate, it was 274 ± 9.0, 246 ± 7 7, and 332 ± 4 9 mg per 100 gm, respectively, compared with 404 ± 7 1 mg. per 100 gm. in control rats. The same authors studied certain aspects of the pharmacology of 3-hydroxy-2-phenylcinchoninic acid. They noted that dialysis of plasma in the dog revealed that more than 95 per cent of the drug was bound to plasma proteins. Fifty milligrams per kilogram per day was administered to two Rhesus monkeys by mouth and for 30 days no toxic symptoms appeared. In man, less than 2 per cent was excreted in 24 hr. after 24 mg per kg orally and less than 3 per cent in the form of total (free and conjugated) drug Oral administration of 200 and 400 mg per kg. daily to young rats for 11 days and 40 mg. per kg. daily to dogs for 30 days produced no toxic symptoms. Eight hundred milligrams per kilogram per day caused the deaths of two of five rats, and 100 mg per kg per day caused lethargy, anorexia, and loss of weight in two dogs after 10 and 12 daily doses and the death of one of the dogs on the twenty-third day At necropsy, both dogs showed areas of denudation in the small intestine, and in one a similar area in the colon.

Lenzner, Lockie & Becker (320) reported acute yellow atrophy following cinchophen administration beginning on the day after the injection of 2 gm. of cinchophen and terminating fatally 12 days later Clinical and pathological evidence of pre-existing hepatic disease was absent. Urinary suppression and early phosphorus retention were featured In addition to the usual picture of cholemic nephrosis, the kidneys showed considerable amounts of calcium in the collecting tubules and their peripheral branchings The report of this case was important since at necropsy no pre-existing liver disease was revealed The possibility of a previous injection of cinchophen could not be eliminated in this instance.

Hartiala *et al.* (321) reported an increase in both the volume and alkali content of pancreatic juice from the dog's pancreas stimulated to secrete submaxilly by continuous intravenous secretin infusion This increase was brought about by the intravenous administration of 100 mg per kg of neutralized sodium cinchophen. The previous oral administration of cinchophen to the point of ulcer production for four days failed to alter the response of the pancreatic secretion to intravenous sodium cinchophen Eiken (322) reported the development of a peptic ulcer in a patient following the ingestion of 15 tablets containing 50 cg of cinchophen and 0 5 mg of colchicine taken one to four times daily. Benjamin (323) reported a case of hepatitis caused by cinchophen and its recovery Hartiala (324), in studying

eight dogs with isolated duodenal fistulae, noted that the effect of feeding cinchophen was the depression of the alkali content and mucin content of the duodenal juice with recovery occurring upon withdrawal of the drug Morphological changes were observed in Breunner's glands but not in the overlying crypts of Lieberkuhn after cinchophen treatment,

McCracken *et al.* (325) reported on the favorable use of cinchophen in 14 cases of gout using a dosage of 1 5 to 3 gm of cinchophen daily for three or four days. They reported no toxic manifestations Kelly and associates (326) reported on the use of cinchophen in 2,500 gout patients intermittently for long periods of time Among these 2,500 cases, they did not note a single case of hepatic damage. They emphasized that cinchophen should not be considered as a general anti-rheumatic agent, since patients with other types of arthritis do not appear to tolerate it as well or in as large amounts as does the patient with gout.

Wrigley (327) re-opened and reviewed the question of the use of glycine (gelatin) in the treatment of chronic gout. His human experiments showed that the ingestion of 25 gm. of glycine by two subjects was found to increase the uric acid output of both. Average uric acid output was 23.4 mg. per min. before administration of glycine and 39 95 mg after or an increase of 71 per cent The average uric acid clearance increased from 11.9 to 17.5 cc. per min., an increase of 47 per cent He encouraged re-evaluation of the use of glycine in chronic gout

Coste *et al* (328) reported that the administration of thiamine by mouth and by vein gave subjective and objective relief in patients with gout, and they advocated its use in cases where colchicine had failed. Violle (329) reported the favorable use of the antihistaminics in the control of gout. Talbott (330) pointed out that the average patient with gout is going to spend about 99 per cent of his time in the interval periods between attacks He feels that the use of the low-purine diet during the intervals between attacks is helpful, but not obligatory During this interval, his patients received colchicine intermittently, one or two tablets a week, and in some instances one per day. A high fluid intake is encouraged to enhance the excretion of uric acid and minimize the chance of kidney involvement. In the experience of the reviewer, the daily administration of coated tablets of sodium salicylate, glycine, plus one or two tablets of colchicine per day affords greatest freedom of acute exacerbation of gout

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ANNOTATED LIST OF REVIEWS IN MEDICINE

By Eaton M. MacKay

Medical Division, E. R. Squibb & Sons, New York, N. Y.

The following list includes the major number of reviews which appeared between November, 1949 and January, 1951 All of them were read and the notes indicate the appeal they made to the reader at the time of reading.

Infectious Diseases

1. "Syphilis," Crawford, G. M., *New Engl. J. Med.*, 243, 916–26, 955–66 (1950), 202 references. A complete review of the subject over the past few years with special reference to penicillin therapy.
2. "Some Properties of Viruses," Andrewes, C. H., *New Engl. J. Med.*, 242, 161–66 (1950), 28 references. A broad consideration of the subject.
3. "Epidemic Influenza," Andrewes, C. H., *New Engl. J. Med.*, 242, 197–203 (1950), 14 references A stimulating, not too technical general review of the subject and problems which it poses.
4. "Recognition, Treatment and Control of Poliomyelitis," Vogel, E, *New Engl. J. Med*, 242, 899–908 (1950), 111 references. A complete critical review of the literature of the past several years and the present status of the disease.
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6. "Brucellosis," Braude, A I., and Spink, W. W., *Advances in Internal Med.*, 4, 163–200 (1950), 76 references. A summary of all phases of the problems of this disease.
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8. "Acute Diarrheal Disorders of Newborn Infants; Differential Diagnosis," Abramson, H, *Am J. Diseases Children*, 79, 698–711 (1950), 28 references A critical review of a confusing ailment.
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10. "Pathogenetic Concepts of Tuberculosis," Medlar, E. M., *Am. J. Med*, 9, 611–22 (1950), 3 references. A review of the subject, not the literature
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14. "Biologic and Immunologic Properties of Tubercle Bacilli," Dubos, R. J., *Am. J. Med.*, 9, 573–90 (1950), 58 references. A beautiful review.

15. "Effects of Antimicrobial Agents on the Tubercle Bacillus and on Experimental Tuberculosis," Steenken, W., Jr., and Wolinsky, E, *Am J. Med.*, 9, 633–53 (1950), 86 references. A complete summary.

16 "Antimicrobial Therapy in Human Tuberculosis," Hinshaw, H. C., *Am J. Med.*, 9, 654–61 (1950), no references. A brief summary of the subject at the date of preparation.

Diseases of the Gastrointestinal Tract

1. "Digestive System," Grossman, M. I., *Ann. Rev. Physiol.*, 12, 205–36 (1950), 228 references. An adequate summary of recent developments.

2. "Surgery of the Esophagus," Strieder, J. W., *New Engl. J. Med*, 243, 445–54 (1950), 63 references. A thorough review of all phases of the subject of interest to the general clinician as well as the specialist.

3. "Hepatitis and Cirrhosis of the Liver," Patek, A J., Jr., *Advances in Internal Med.*, 4, 329–56 (1950), 49 references. A fair presentation of the subject as of the present time.

4 "Primary Biliary Cirrhosis," Ahrens, E. H., Jr., Payne, M. A, Kunkel, H G., Eisenmenger, W. J., and Blondheim, S. H., *Medicine*, 29, 299–364 (1950), 157 references. A complete coverage of the literature with data on a new series of patients included.

5 "Abdominal Surgery," Allen, A. W., and Welch, C. E., *New Engl. J. Med*, 243, 16–23 (1950), 84 references A brief summary of developments during the past two years.

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Diseases of the Cardiovascular System

1. "Heart," Hemingway, A., *Ann. Rev Physiol.*, 12, 345–68 (1950), 159 references. Of as much interest to the cardiologist as the physiologist. Recent literature is covered in a critical manner

2. "The Genesis of Heart Sounds," Orias, O, *New Engl J Med*, 241, 763–69 (1949), 78 references An interesting historical and critical review.

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4. "The Peripheral Circulation," Edholm, O. G., *Ann Rev. Physiol*, 12, 311–44 (1950), 315 references. Particularly useful as a source of new

developments for the interested clinician as well as the investigator.

5. "Cardiac Aneurysm," Berman, B and McGuire, J., *Am. J. Med.*, 8, 480–88 (1950), 39 references A review of the literature and a new series of cases.

6. "The Relation of Cholesterol to the Development of Atherosclerosis," P. W. Clough, *Ann. Internal Med*, 33, 250–58 (1950), 31 references A brief critical summary of current research and clinical knowledge

7. "Clinical Use of Anticoagulants," Estes, J. E, and Allen, E V., *Advances in Internal Med*, 4, 297–327 (1950), 38 references. A detailed consideration of the subject presented in a manner useful for the practitioner.

8. "Cardiac Catheterization," Ellis, L. B, and Bloomfield, R. A., *New Engl J. Med*, 243, 339–45 (1950), 79 references. A concise review of a subject of interest to the clinical investigator.

9. "The Vascular Physiology of Hypertension," Pickering, G. W., *Advances in Internal Med.*, 4, 445–504 (1950), 166 references. A review which indicates how little we yet know about hypertension

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11. "The Dietetic Treatment of Hypertension and Nephritis," P. W. Clough, *Ann. Internal Med.*, 32, 989–95 (1950), 10 references. A fair review of the provocative subject

12. "The Diet and Hypertension," Chapman, C B., and Gibbons, T B, *Medicine*, 29, 29–69 (1950), 226 references. A fair but critical review of a topic which has recurred at intervals for 50 years and is currently of wide interest

13. "Role of Sympathetic Blockage in the Therapy of Hypertension," Nickerson, M., *Am J. Med*, 8, 342–54 (1950), 103 references A brief summary of a subject now holding the attention of many investigators.

14. "Portal Hypertension," Welch, C. S., *New Engl. J Med*, 243, 598–610 (1950), 71 references A review of all recent literature

15. "The Evaluation of Cardioactive Agents by Human Bioassay," Shane, S J, *New Engl J Med*, 243, 740–47 (1950), 28 references A critical study of a very important problem in therapeutics.

Diseases of the Urinary System

1 "Kidney," Trueta, J, *Ann Rev. Physiol*, 12, 369–98 (1950), 190 references A summary of recent literature for the clinical physiologist as

" Earle, D. P, *Am. J.*
entation of a complex field with special reference to the diseased kidney.

3 "An Essay Toward a Dynamic Morphology of the Mammalian Nephron," Oliver, J., *Am J Med*, 9, 88–101 (1950), 27 references A brief résumé of a classical development in modern pathology.

4 "Tubular Transport Mechanisms," Taggart, J. V., *Am. J. Med.*, 9,

678–90 (1950), 95 references A thorough and critical consideration of this phase of renal physiology.

5. "Acid-Base Regulation by the Kidneys," Pitts, R. F., *Am. J. Med*, 9, 356–72 (1950), 45 references. A fine summary from the point of view of clinical physiology.

6. "Renal Excretion of Water, Sodium, Chloride, Potassium, Calcium and Magnesium," Berliner, R. W., *Am. J. Med.*, 9, 541–59 (1950), 143 references. An excellent résumé of this phase of renal physiology.

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8. "Significance of the Renal Juxtamedullary Circulation in Man," Maxwell, M. H., Breed, E. S., and Smith, H. W., *Am. J. Med.*, 9, 216–28 (1950), 49 references. A critical study of a frequently argued point.

9. "Peritoneal Lavage as an Effective Means of Extrarenal Excretion," Odel, H. M., Ferris, D. O., and Marschelle, H. P., *Am. J. Med.*, 9, 63–77 (1950), 53 references. A clinical appraisal of a new therapeutic approach

10. "Medical Aspects of Pyelonephritis," Birchall, R, and Alexander, J. E., *Medicine*, 29, 1–28 (1950), 164 references. A summary of the ailment as an entity which demands a stated therapy routine.

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DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HEMATOLOGY

1. "Vitamin B_{12} and Pernicious Anemia," Strauss, M. B., *New Engl. J. Med.*, 243, 187–94, 222–29 (1950), 176 references A critical review covering all facets of the subject.

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4. "The Coagulation of Blood and Hemostasis," Quick, A J, *Ann Rev. Physiol.*, 12, 237–64 (1950), 267 references. A review of interest to the clinician as well as the investigator.

NUTRITION AND NUTRITIONAL DISEASES

1. "Energy Metabolism," Chambers, W. H, and Summerson, W H, *Ann Rev. Physiol.*, 12, 289–310 (1950), 104 references. Excellent

2. "Water Metabolism," Elkinton, J R, *Ann. Rev Physiol*, 12, 145–78 (1950), 199 references A critical and complete review of the literature suitable for the clinical investigator as well as the physiologist.

3. "Analysis of Foods by Sensory Difference Tests," Boggs, M M, and Hanson, H. L., *Advances in Food Research*, 2, 219–58 (1949), 72 references A survey of our present knowledge with a careful study of the value of different tests.

4. "Body-Fluid Physiology· The Role of Potassium in Clinical Disturbances of Body Water and Electrolyte," Darrow, D C., *New Engl. J.*

Med, 242, 978–83, 1014–18 (1950), 83 references. All phases of disturbed potassium metabolism are considered in detail.

5. "Season, Nutrition and Pellagra," Sargent, F., 2nd, and Sargent, V. W., *New Engl. J. Med.*, 242, 447–53, 507–14 (1950), 84 references An excellent review of interest to anyone concerned with nutrition.

6. "Present Status of Caries Control and Caries Prevention," Massler, M., *Med. Clinics N. Amer.*, 34, 13–32 (1950), 36 references. A fair critical review of a controversial topic.

7. "Nutrition and Disease of the Liver," Davidson, C. S., and Gabuzda, G J., Jr., *New Engl. J. Med*, 243, 779–88 (1950), 100 references. A critical evaluation of current therapy.

8. "The Versatility of Adipose Tissue," H. J. L. M., *Ann. Internal Med*, 32, 162–66 (1950), 21 references. A general review of adipose tissue as an organ.

9 "Self-Demand Feeding," Weinfeld, G F., *Med Clinics N. Amer.*, 34, 33–40 (1950), no references. An interesting discussion of the subject

10 "Parenteral Fluid Therapy in Children," Hand, A. M., and Leininger, C. R, *Med. Clinics N. Amer.*, 34, 53–70 (1950), 21 references. A practical, usable summary.

11 "The Management of Obesity in Childhood," Steiner, M M, *Med. Clinics N. Amer.*, 34, 223–34 (W. B. Saunders Co., Philadelphia, January, 1950), 19 references. A brief review of approved procedure.

Endocrinology

1. "The Adrenal Cortex and Homeostasis," Sayers, G, *Physiol Revs*, 30, 241–320 (1950), 519 references A critical study of all the literature bearing on this subject

2. "Metabolic Functions of the Endocrine Glands," Tepperman, J., and Tepperman, H. M., *Ann Rev. Physiol.*, 12, 503–36 (1950), 200 references An excellent review of recent contributions.

3. "The Virilizing Syndrome in Man," Soffer, L. J, Gabrilove, J. L, Jailer, J. W, and Jacobs, M D, *Recent Progress Hormone Research*, 5, 407–38 (1950), 88 references. A good clinical summary.

4. "Experimental Endocrine Tumors with Special Reference to the Adrenal Cortex," Woolley, G W., *Recent Progress Hormone Research*, 5, 383–405 (1950), 34 references. An interesting summary.

5. "Addison's Disease," Sorkin, S. Z, *Medicine*, 28, 371–425 (1949), [illegible] this malady

[illegible] R., Robert- [illegible] 57 (1950), 15 references A complete summary of the subject, including symptoms, signs, and diagnostic procedures.

7. "Sympathetic Hormonal Transmission," Tainter, M. L, and Luduena, F P., *Recent Progress Hormone Research*, 5, 3–35 (1950), 151 references A critical review of a subject which is currently of unusual interest.

8. "Factors Affecting the Control of the Pituitary Gland," Noble, R. J., Plunkett, E. R., and Taylor, N. B. G., *Recent Progress Hormone Research*, 5, 263–304 (1950), 116 references. A thorough review of interest to the clinician and investigator alike.

9. "Steroid Control of Pituitary Function," Greep, R. O., and Jones, I C., *Recent Progress Hormone Research*, 5, 197–261 (1950), 36 references A review of the literature with added new data.

10. "Nutrition and Goiter," Greer, M A., *Physiol. Revs.*, 30, 513–48 (1950), 125 references. A critical study of a much debated subject.

11. "Experimental Diabetes," Sacks, M. S., *Ann. Internal Med.*, 32, 572–76 (1950), 25 references An up-to-date review which covers all current aspects of the subject in a small space.

12. "Diabetes Mellitus," Beaser, S. B., *New Engl. J. Med.*, 243, 81–85, 133–37 (1950), 114 references. A review which brings all phases of the problem up-to-date.

13 "Diabetic Coma," Butler, A. M , *New Engl. J. Med.*, 243, 648–59 (1950), 149 references. A review of the physiological basis of diabetic coma and its therapy.

14. "Functioning Pancreatic Islet Cell Adenomas," Crain, E. L., Jr., and Thorn, G. W., *Medicine*, 28, 427–47 (1949), 158 references. A review of the past literature and consideration of diagnostic tests.

15. "The Effect of the Hyperglycemic Factor of the Pancreas and of Epinephrine on Glycogenolysis," Sutherland, E R., *Recent Progress Hormone Research*, 5, 441–63 (1950), 28 references. A review of biochemical investigations.

16 "Reproduction," Asdell, S. A , *Ann. Rev Physiol*, 12, 537–56 (1950), 190 references An adequate summary of the present status of the physiology of reproduction.

17 "Androgenic Activity of the Ovary," Parkes, A. S., *Recent Progress Hormone Research*, 5, 101–14 (1950), 32 references An excellent brief summary

18. "The Vasculature of the Ovary and Ovarian Function," Reynolds, S. R. M , *Recent Progress Hormone Research*, 5, 65–100 (1950), 17 references. A thorough review of a complex subject

19. "Maintenance of the Corpus Luteum and Physiologic Actions of Progesterone," Bradbury, J. T., Brown, W. E., and Gray, L. A., *Recent Progress Hormone Research*, 5, 151–94 (1950), 83 references. An excellent review of the subject.

20. "Some Aspects of the Physiology of Estrogenic Hormones," Paschkis, K. E., and Rakoff, A. E , *Recent Progress Hormone Research*, 5, 115–49 (1950), 160 references. An extremely useful summary for a worker in any field.

21. "Gastrointestinal Hormones," Grossman, M. I., *Physiol Revs*, 30, 33–90 (1950), 482 references. A complete, very critical summary of a confused subject.

22. "Hormone-Enzyme Relationships," Meyer, R. K , and McShan,

W. H., *Recent Progress Hormone Research*, 5, 465–515 (1950), 157 references. A review of a specialized subject intended for the biochemist.

Allergy

1. "Allergy," Burrage, W. S., *New Engl J. Med.*, 243, 50–53 (1950), 42 references. A very brief review of new therapy.

2. "The Role of Allergy in the Pathogenesis of Rheumatic Fever," Fischel, E. E., *Am J. Med*, 7, 772–93 (1949), 288 references. A timely critical review.

Neoplastic Diseases

1. "Neoplastic Infection and Cancer," Duran-Reynals, F, *Am. J. Med*, 8, 490–511 (1950), 100 references An interesting review of the pertinent literature.

2. "Cryptococcosis," Gendel, B. R, Ende, M., and Norman, S. L, *Am. J. Med*, 9, 343–55 (1950), 81 references. A review of our knowledge of this fungus infection with special reference to Hodgkin's disease.

3. "Hepatic Manifestations of Sarcoidosis and other Granulomatous Diseases," Klatskin, G, and Yesner, R., *Yale J. Biol. Med*, 23, 207–48 (1950), 88 references. An extensive original study and a review of the literature

4 "An Introduction to Cancer Research," Mider, G B, *Am. J. Med.*, 8, 71–89 (1950), 140 references An interesting summary.

5. "Biochemistry of Melanin Formation," Lerner, A. B, and Thomas, B. F, *Physiol. Revs*, 30, 91–126 (1950), 179 references A study of interest to specialist investigators

6. "Genetic Aspect of Cancer Research," Bittner, J. J., *Am. J. Med*, 8, 218–28 (1950), 85 references A careful review of a subject increasingly interesting to workers in the field of human neoplasms

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